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CEREBRAL EMBOLISM FOLLOWING MINOR WOUNDS OF THE CAROTID ARTERY

Report of an Autopsy

AIDAN A. RANEY, M.D.*
LOS ANGELES

IT HAS long been known that serious consequences may follow trauma or ligation of the carotid artery. About 1798 Abernathy[1] ligated the common carotid artery in a patient who had been gored in the neck by an ox, in order to arrest bleeding from a lacerated left internal carotid artery; the right side was paralyzed, and the patient died thirty hours after ligation. The common carotid artery was ligated in England by Fleming and in America by Cogswell in 1803; in the first instance the patient survived, while the latter case ended fatally twelve days after operation.[2] For the treatment of aneurysm, ligation of the common carotid artery was first employed by Cooper[3] in 1805; hemiparesis developed on the eighth day, to be followed thirteen days later by death. However, in all fairness, it should be added that three years later this surgeon repeated the same procedure successfully in a similar case and the patient lived an additional thirteen years.

The advent of aseptic surgery produced on appreciable change in the incidence of cerebral complications following ligation of the carotid artery.[2] The incidence varies according to the type under consideration and other factors, but generally it is from 20 to 30 per cent.[4] Evidently Jackson[5] was referring to accidental injury rather than to surgical trauma when he remarked that "degenerative processes within the brain traceable to injury in the neck are few and far between and are to be classed

* Formerly Lieutenant Colonel, Medical Corps, Army of the United States.

1. Abernathy, cited by DaCosta,[25b] p. 389.

2. Pilcher, C., and Thuss, C.: Cerebral Blood Flow, Arch. Surg. **29**:1024-1038 (Dec.) 1934.

3. Cooper, A., cited by DaCosta,[25b] p. 389.

4. Jordan, cited by DaCosta,[25b] p. 390. Pilcher and Thuss.[2] Reid, M. R., and Andrus, W. de W., in Nelson's Loose-Leaf Living Surgery, New York, Thos. Nelson & Sons, 1941, vol. 1, pp. 647-780.

5. Jackson, H., in Maingot, R.; Slesinger, E. G., and Fletcher, E.: War Wounds and Injuries, ed. 2, Baltimore, Williams & Wilkins Company, 1943, p. 499.

among pathological curiosities." It would seem that such a statement refers to the relative rarity of primary injury to the carotid artery rather than to the infrequency of degenerative complications subsequent to such traumatism.

Several explanations have been advanced for cerebral manifestations following local occlusion of the common or internal carotid artery. Simple digital occlusion for a period not exceeding eight seconds was found[6] to produce cerebral signs, which in the particular case under observation were obviously due to cerebral ischemia and an anomalous circle of Willis and should not be mistaken for a hyperactive carotid sinus reflex. If, before the ligation of the carotid artery, the circle of Willis has been proved adequate for collateral blood supply to the hemisphere, but if, nevertheless, cerebral complications follow ligation, they must be explained on the basis of thrombus formation at the site of ligation and subsequent distal extension, leading either to thrombosis of the circle of Willis or, as originally suggested by Perthes,[7] to detachment of fragments and embolic occlusion of the cerebral branches.

In cases of cerebral complications following wounds of the carotid artery in which the blood-carrying capacity of the carotid arteries has not been critically reduced, cerebral embolism arising from a mural thrombus in the carotid artery at the site of injury must be considered as a cause of cerebral complications, regardless of whether the circles of Willis is complete or not. But cerebral complications in cases in which the circle of Willis is adequate, whether the injured carotid artery is occluded or not, may be due either to embolism, as already described, or to a thrombus extending into the circle of Willis.

The origin of emboli from mural thrombi of large arteries or aneurysms in other parts of the body has frequently been reported.[8] Thrombi developing in the systemic venous channels or in the pulmonary artery are generally filtered out and immobilized by the pulmonary screen, thereby preventing them from reaching more vulnerable tissues. However, even here they do not always prove to be harmless, as pulmonary embolism is accountable for approximately 6 per cent of the fatalities occurring after major surgical procedures.[9] When emboli are liberated in

6. Marsh, C., and Raney, A. A.: Electroencephalographic Findings in Transitory Cerebral Anemia: Jacksonian Seizures Due to Digital Occlusion of Internal Carotid Artry in Attempted Treatment of Carotid Cavernous Aneurysm, Bull. Los Angeles Neurol. Soc. **7**:39-42 (March) 1942.

7. Perthes, G., cited by Lipshütz.[13]

8. Hoobler, S. W.: Syndrome of Cervical Rib with Subclavian Arterial Thrombosis and Hemiplegia Due to Cerebral Embolism: Report of Case, New England J. Med. **226**:942-944 (June 11) 1942.

9. Priestley, J. T., and Barker, N. W.: Postoperative Thrombosis and Embolism: Their Treatment with Heparin, Surg., Gynec. & Obst. **75**:193-201 (Aug.) 1942.

the pulmonary veins, as may occur in cases of carcinoma of the lung, pulmonary abscess, penetrating wounds of the lung or "blast injury" of the lung, they may travel unimpeded to the left side of the heart, from whence they may continue to the brain and produce cerebral lesions, such as cerebral metastases, encephalitis, cerebral abscess, cerebral embolism or an embolic process sometimes erroneously diagnosed as "blast concussion of the brain." Indeed, cerebral embolism is of such common occurrence in cases of pulmonary abscess, carcinoma of the lung, fracture of the femur, mitral stenosis and auricular fibrillation that it is always to be suspected as a cause of any cerebral complication developing in the course of such illnesses.

The incidence of thromboembolism subsequent to wounds of the carotid artery is probably as great as in any of the aforementioned conditions. Bailey[10] stated:

> It should be realized that quite a large proportion of patients with wounds of the great vessels of the neck, who have been spared to reach surgical aid have died, not from the effects of hemorrhage nor of shock consequent upon surgical intervention, but from embolism located at necropsy in the circle of Willis.

Holman[11] recognized that contusion of an artery may result in embolism. The intima is the most vulnerable coat of the arterial wall,[12] and injury of the intima is one of the chief causes of intravascular clotting.[13] Such damage to the intima leading to thrombus formation, may be caused by nothing more than stretching of the carotid artery.[14] One of the factors determining the size of the resulting thrombus is the extent of damage inflicted on the intima, so that a minimal injury may produce only a small mural thrombus which will not occlude the lumen. However, the blood stream may tear a small thrombus from its point of origin at the site of injury to the vessel, thus causing embolism.[13] De Takats[15] stated that postmortem examinations prove that from 50 to 70 per cent of all thrombi develop into emboli. Newly formed thrombi are more readily detached than older, well organized clots, and it is probable that a thrombus in a vessel situated in the neck or near a joint is more likely

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10. Bailey, H.: Surgery of Modern Warfare, Baltimore, Williams & Wilkins Company, 1941, vol. 1, pp. 297-318.

11. Holman, E.: War Injuries to Arteries and Their Treatment, Surg., Gynec. & Obst. **75**:183-192 (Aug.) 1942.

12. Lexer, E.: General Surgery, New York, D. Appleton & Company, 1908, pp. 549-550.

13. Lipshütz, B.: Injuries of Large Arteries Encountered in Civil Practice, Surg., Gynec. & Obst. **46**:62-71 (Jan.) 1928.

14. Moniz, E., cited by Eckers, A. H.: Spasm of Internal Carotid Artery, J. Neurosurg. **2**:479-484 (Nov.) 1945.

15. de Takats, G., in Christopher,[27] pp. 202-209.

to release an embolus than if the injured vessel were in a position less exposed to external disturbances.

As secondary embolism so readily results from thrombosis, it may well be surprising that its presence is not more frequently noted. But several factors contribute to the diagnostic difficulties. De Takats[15] expressed the belief that "small emboli probably break loose often, but are symptomless." This could easily occur in many regions of the body where collateral circulation is adequate to compensate before significant signs or irreparable damage can develop. The central nervous system, on the other hand, is less tolerant to occlusion of even small arteries; however, in relatively silent areas of the brain occlusion may occur with little, if any, evidence betraying its presence.

Even though statistics may not be available to substantiate this point, it is likely that in war casualities cerebral complications follow trauma of the carotid artery more frequently than in cases of wounds encountered in civilian practice. Those who have experienced, during the active phases of a military campaign, a heavy patient load in medical installations will agree that it is unavoidable that the less pronounced cerebral complications may go unrecognized, especially if no conspicuous manifestations cause the examiner to be particularly alert for signs of cerebral disturbance. Before such a patient reaches a station down the line of evacuation, where a more specific examination can be carried out, the indicative symptoms and signs may have subsided beyond recognition.

Accidental wounds of the neck involving the soft tissues are uncommon in civil practice. In one large metropolitan hospital no more than 12 fresh, accidental wounds of the soft part of the neck, anterior or lateral, were treated over a period of seventeen years.[16] The infrequent occurrence of wounds of the carotid region in civilian practice must be attattributed to the fact that the carotid artery is a relatively short vessel, deeply situated and in a position where the natural reflexes tend, in time of apparent danger, to increase that protection. Furthermore, nonmilitary accidental wounds in the carotid region are usually caused by sharp instruments such as fragments of glass, knives or razors, which cause little damage to tissues other than those actually incised; consequently, any such wound that affects the intima of the carotid artery is more likely to result in rapidly fatal hemorrhage than in partial or complete thrombosis of the artery.

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16. Hanford, J. M., in Christopher,[27] pp. 818-822.

17. The patients whose cases are reported here were seen by me in the neurosurgical service of an evacuation hospital in the European combat zone. Often the heavy patient load delayed, or even prevented, complete and detailed examination, as well as the making of notes. Furthermore, some of the data were subsequently lost in the tides of war.

REPORT OF CASES[17]

CASE 1.—*Penetrating wound in right pharyngomaxillary space; left hemiplegia; fistula of carotid artery and jugular vein; carotid arteries remaining patent; circle of Willis adequate.*

A soldier, wounded in Germany on Sept. 17, 1944, sustained injuries which were initially diagnosed as a wound of the right cheek due to a shell fragment and possible head injury. Later, on admission to this evacuation hospital, he was comatose; treatment for shock resulted in improvement of his condition, although he remained irrational and irritable. With the patient under "pentothal" anesthesia, Capt. M. J. Ryan debrided the wound of entry, measuring 1 cm., in the right cheek, although the foreign body in the right pharyngomaxillary space could not be removed. On the following day the patient was comatose and had spastic left hemiplegia. Studies of the spinal fluid revealed an essentially normal state. During the succeeding three days, pneumonia, which developed, was successfully treated with sulfonamide drugs, penicillin and other agents. Three days after injury thrill and bruit were discovered. The bruit, present in the carotid and temporal areas, was continuous, but more pronounced during systole, and could be terminated by digital occlusion of the ipsilateral common carotid artery. Continuous occlusion of either common carotid artery for a few minutes produced no additional cerebral signs.

On regaining consciousness, the patient interpreted the bruit as "coming from a ventilating system in the tent." On the eighth day after injury, when he was transferred to a general hospital, his mental status had improved satisfactorily, although recovery from the hemiplegia was less rapid.

Comment.—Failure of digital occlusion of either carotid artery to produce additional cerebral signs indicates not only that the injured carotid artery and the circle of Willis were patent, but also that the cerebral disturbances were not attributable to temporary carotid spasm or to any other type of occlusion of the carotid artery. Obviously, the cerebral disturbances had been produced by a pathologic process distal to the circle of Willis, and it is probable they were due to cerebral embolism subsequent to mural thrombosis of the carotid artery.

CASE 2.—*Laceration of left internal jugular vein and perforation of left common carotid artery, resulting from penetrating shell fragment; right hemiplegia and aphasic disturbance.*

On Oct. 14, 1944, the soldier was admitted to this evacuation hospital, three hours after a shell fragment had penetrated the left side of the neck. He was mentally sluggish and had right hemiplegia, in addition to a laceration, measuring 2 cm., of the neck. The pulsation of the left temporal artery was palpable, although weaker than that of the right. Later he responded sluggishly and was able to give his name. Operation was performed by Major V. P. Blair and Lieut. Col. C. H. Avent six hours after injury, with the patient under general anesthesia. Examination revealed paralysis of the left vocal cord. During preparation of the patient, severe arterial bleeding occurred from the wound in the neck and was controlled by pressure. The metallic fragment, measuring 1 by 1 by 2 cm., was found in the carotid sheath and removed. The hemorrhage was observed to originate from a laceration of the common carotid artery, measuring 0.5 cm. and lying approximately 3 cm. caudal to the bifurcation; this laceration was sutured, and the severely lacerated jugular vein was ligated.

Twelve hours after operation the patient was mentally sluggish, responding to moderately painful stimulation; by this means it was possible to obtain answers to one or two questions before fatigue developed. His voice was husky and enuncitation poor. There was conjugate deviation of the eyes to the left but occasionally he turned his eyes toward the right. Right homonymous hemianopsia was evidently present. The right hemiplegia was spastic in all parts except the wrist, which was flaccid. A Horner syndrome was present on the left.

During the succeeding five days the patient become fairly alert mentally and interested in his surroundings. His voice was low, suggesting continued dysfunction of the vocal cord, although otherwise he spoke fairly well. There were no grossly demonstrable visual field defects at that time, and the eyes at rest were in a neutral position, although there was some difficutly in turning the eyes to the right. He had slight difficulty in naming animate objects and made several mistakes in identifying colors. He recognized numbers, letters and most symbols. There was slight acalculia. He was practically unable to draw geometric figures but was able to write with either hand, although the right was weak and clumsy. There was no confusion of laterality; however, moderate finger agnosia was present. He insisted that he was able to read without lip movement; however, he was unable to grasp the meaning unless he was permitted to read aloud. Stereognostic sense and two point discrimination were considerably impaired on the right side of the body. At this time there was right hemiparesis. Function of the individual fingers of the right hand was almost completely lost. However, the grip of the right hand was fairly strong.

Nine days after the injury, examination revealed continued improvement. The patient made fewer mistakes in recognizing and naming colors and symbols. There was considerable residual dyscalculia. Stereognostic sense and two point discrimination were essentially unchanged. The spastic right hemiparesis had improved only slightly. He was evacuated to a general hospital, and notes of his later progress are not available.

Comment.—Operation revealed neither occlusion nor spasm of the carotid artery, yet before operation cerebral signs were present. It was not possible to ascertain the mechanism responsible for the development of the cerebral signs; but, as laceration of the carotid artery had set the stage for mural thrombosis, secondary cerebral embolism is the most probable cause of the cerebral disturbances.

CASE 3.—*Small penetrating wound in region of carotid artery; contralateral hemiplegia; wounds of lower extremities; no visible local evidence of head injury.*

A soldier, wounded in the Ardennes in December 1944, arrived a few hours later at this evacuation hospital, where examination revealed multiple wounds of the lower extremities and a single small penetrating wound in the neck. With treatment for shock the patient's condition failed to improve. The appearance of neurologic signs suggested the presence of an associated head injury. Neurologic examination revealed hemiplegia contralateral to the wound in the neck. Examination failed to reveal signs consistent with occlusion of the carotid artery. The wound in the neck was not actively bleeding, and there was no hematoma. Examination of the head revealed no laceration, abrasion, contusion or other evidence of direct head trauma. The clinical impression at the time of the examination was that the cerebral lesion was secondary to the injury of the carotid artery, although not the result of occlusion of that artery.

Comment.—The presence of unilateral cerebral signs indicated that the cerebral phenomena were attributable to injury of the ipsilateral carotid artery; yet the findings indicated that the affected carotid artery was patent. The most probable explanation of the cerebral lesion is cerebral embolism secondary to injury and mural thrombosis of the carotid artery.

CASE 4.—*Mortar shell fragment, penetrating left side of neck, found at operation lying on anterior surface of carotid artery; aphasia and right hemiparesis.*

On Feb. 24, 1945, a soldier, aged 30, was received at this evacuation hospital with an initial diagnosis of penetrating wound of the neck due to a mortar shell fragment. Nine hours after injury Capt. M. J. Ryan removed the fragment, observed lying on the bifurcation of the left carotid artery. The great vessels were intact, and pulsation of the artery was normal. On the following day the patient appeared alert but could not grasp the meaning of rapidly spoken language. He could see objects in the right visual field but could not accurately count fingers there, seemingly being unable to focus his attention on them. He accurately followed objects from right to left but not from left to right. He had confusion of laterality, finger agnosia, acalculia, right hemiparesis (affecting principally the hand and fingers) and right hemihypesthesia, with impairment of two point discrimination, stereognosis and position sense. On the left side Horner's syndrome was present.

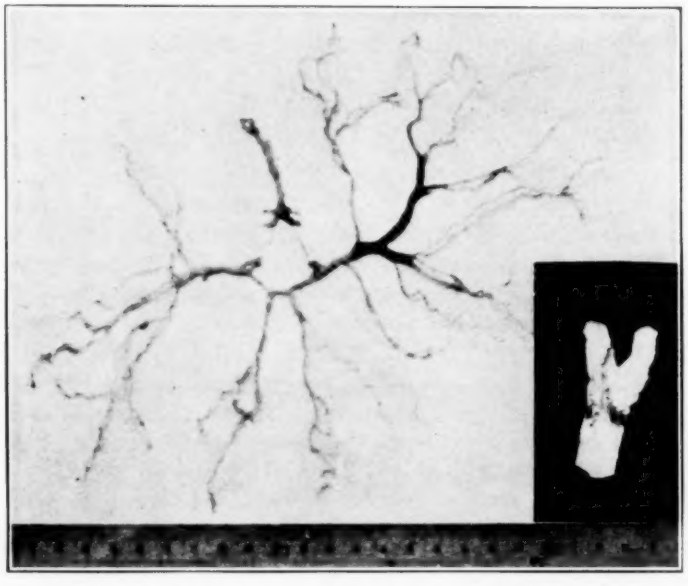
Examination three days after injury revealed considerable improvement. He was more attentive to objects held in the right visual field, although a green toothbrush held in the right field was identified as a "blue fountain pen," but the object was quickly and correctly identified when held in the left visual field. Acalculia and ginger agnosia had subsided. The hemiparesis had improved slightly, although the patient was unable to manage a cigaret, even with the left hand, the strength of which was unimpaired. The patient was transferred to a general hospital on the fourth day after injury, and further notes of his progress are not available.

Comment.—Operation failed to show laceration, spasm or thrombotic occlusion of the artery. The most logical explanation for the cerebral signs is embolism from a mural thrombus of the carotid artery. Riddoch's syndrome and apraxia were interesting features of this case.

CASE 5.—*Shell fragment penetrating left side of chin, fracturing mandible and extending to left carotid artery. Death twenty-two hours after injury. Autopsy; small mural thrombus of carotid artery and embolism of left middle cerebral artery.*

A soldier was wounded by a mortar shell fragment on Feb. 28, 1945, while fighting in Germany. The initial diagnosis was compound fracture of the mandible and cerebral concussion. Sulfanilamide powder and dressings were applied to the wound on the left side of the chin, and morphine sulfate, ½ grain (30 mg.), was administered hypodermically. Six hours later the concussion was diagnosed as moderately severe, the pulse was 140 per minute, and the blood pressure was 60 systolic and 40 diastolic. After a blood transfusion the blood pressure was 96 systolic and 50 diastolic and the pulse rate was 92 per minute. The patient was stuporous.

After the patient's arrival at this evacuation hospital, nineteen hours after injury, the blood pressure was 120 systolic and 60 diastolic, the pulse rate 120, the rectal temperature 100.2 F. and the respiratory rate 28. The pulsation of the carotid artery was palpable at the depth of the tract through the chin, and the pulsation of the temporal artery was strong. There was no evidence of trauma of the head. In his comatose condition, his corneal reflexes were still present, but his extremities were flaccid at rest. On painful stimulation, he moved his left arm weakly. During the next two hours his respirations became rapid and his face flushed. He died twenty-two hours after injury.



Actual photograph in case 5, showing the cerebral vessels not retouched in any way. The darkened segment of the middle cerebral artery and branches is the site of the intravascular clot.

In the inset, the carotid artery at its bifurcation has been split longitudinally, exposing small areas of discoloration due to damage of the intima. Loosely attached to these damaged areas are small mural thrombi.

Autopsy.—The mandible was comminuted in the line of the tract from the chin to the sheath of the left carotid artery. The external surface of the great vessels was contused. An area of hemorrhagic contusion, measuring 5 by 7 mm., was observed in the intima of the common carotid artery (figure, inset). No additional damage of the great vessels could be seen. Examination of the brain revealed the left hemisphere to be larger than the right, and there was flattening of the convolutions with signs of herniation of the cingulate gyrus, hippocampal gyrus and cerebellar tonsils.

In the left middle cerebral artery (fig.) 2 cm. distal to its origin, there was observed an intravascular clot, extending 5 cm. along a major branch and with extensions of 0.6 and 1.2 cm. along minor branches. The middle portion of the clot was grayish yellow. Microscopic examination, by Major M. Bevilacqua, revealed the presence of antemortem thrombus in all sections of the affected

cerebral artery. Sections taken at the large bifurcation of the middle cerebral artery revealed organization of the clot and hemorrhage and mechanical disruption of the wall itself.

Comment.—There can be little doubt that the minor wound of the carotid artery led to the formation of a mural thrombus, fragments of which obstructed the middle cerebral artery. After lodgment of the embolus, evidently at the major branching of the middle cerebral artery, proximal and distal thrombosis was superimposed. The size of the communicating arteries of the circle of Willis is of no practical concern in this case because of the location of the site of obstruction.

GENERAL COMMENT

It is of utmost importance to recognize the possible relation of wounds of the neck and cerebral involvement. The diagnostician's alertness to this possibility may spare the patient the additional trauma incident to intracranial exploration. Ordinarily, cerebral embolism is unlikely to simulate a condition in which intracranial surgical intervention would be required. However, circumstances such as the presence of a linear fracture of the skull or wounds of the scalp may suggest that intracranial exploration is indicated. Impairment of loss of function of the intracranial structures may be simulated or produced by the following types of traumatic lesions in the neck:

1. Wounds involving the spinal cord or spinal canal. Traumatic lesions of these structures, capable of producing bizarre neurologic syndromes, are usually readily identified by careful examination.

2. Wounds involving the subclavian or vertebral arteries. Intracranial disturbances resulting from such wounds are rare. Hoobler[8] reported a case of thrombosis of the subclavian artery with embolism reaching the intracranial structures through the right vertebral artery. The location of the injury indicates the vessel most likely to be involved. It is highly improbable that the effects of trauma of these vessels would be confused with those of trauma of the carotid artery.

3. Involvement of the autonomic nervous system. The relatively insignificant cerebral signs resulting from surgical or accidental trauma of the sympathetic or parasympathetic nerves bears evidence that manifestations of severe cerebral dysfunction require explanation on another basis. Stimulation of the sympathetic nerves produces weak vasoconstriction.[18] Such vasoconstriction does not produce serious cerebral signs, and

18. Forbes, H. S.: Physiologic Regulation of Cerebral Circulation, Arch. Neurol. & Psychiat. **43**:804-814 (April) 1940.

it is doubtful whether traumatic stimulation plays any part in the production of cerebral symptoms.[19]

4. Carotid sinus reflex. Stimulation of a hypersensitive carotid sinus may produce cerebral symptoms.[20] The cerebral type of response may consist in dizziness, weakness, faintness, pallor of the face and loss of consciousness; however, the reaction is characterized by complete recovery, and the chain of symptoms seldom persists more than fifteen minutes.[21] The overactivity is usually functional, and no pathologic changes can be noted.[22] During syncope, electroencephalographic examination fails to reveal any gross disorder of the cortical rhythm, such as has been demonstrated in the presence of cerebral ischemia.[6]

Askey[23] reported 10 cases collected by members of the California Heart Association in which stimulation of the carotid sinus was followed by significant complications. In 7 of these cases hemiplegia occurred, evidently as a direct result of mechanical stimulation. However, since the majority of the patients were hypertensive or arteriosclerotic, it is possible that these complications were due to causes other than the carotid sinus reflex, and perhaps even to mechanical disruption of the sclerotic vessel wall, followed by thrombosis or embolism.

5. Vasospasm. In reviewing the literature on vascular spasm, one is impressed with the need for standardization, clarification and definition of terms. Even though the subject has been discussed under a score of terms, practically identical expressions are at times employed to indicate widely differing clinical states.[24] One, therefore, is not surprised to find that the duration of post-traumatic vasopasm is reported variably from a few seconds to more than a year, or to note similar apparent disagreement as to the extent to which vasopasm interferes with the flow of

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19. Dorrance, G. M.: Ligation of Great Vessels of Neck, Ann. Surg. **99**: 721-742 (May) 1934.

20. Forster, F. M.; Roseman, E., and Gibbs, F. A.: Electroencephalogram Accompanying Hyperactive Carotid Sinus Reflex and Orthostatic Syncope, Arch. Neurol. & Psychiat. **48**:957-967 (Dec.) 1942.

21. Ferris, E. B.; Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on Mechanism of Unconscious State and Convulsions: Study of Thirty-Two Additional Cases, Medicine **14**:377-456 (Dec.) 1935.

22. De Graff, A. C., in Cecil, R. L.: Textbook of Medicine, ed. 5, Philadelphia, W. B. Saunders Company, 1940, pp. 1145-1146.

23. Askey, J. M.: Hemiplegia Following Carotid Sinus Stimulation, Am. Heart J. **31**:131-137 (Feb.) 1946.

24. (*a*) Montgomery, A. H., and Ireland, J.: Traumatic Segmentary Arterial Spasm, J. A. M. A. **105**:1741-1746 (Nov. 30) 1935. (*b*) Pratt, G. H.: Surgical Management of Traumatic Lesions of Arteries, S. Clin. North America **23**:358-376 (April) 1943.

blood through the affected vessel.[25] This discrepancy is an indication not so much of controversy as of the need for standardization of terms. Vasospasm is a natural and common response to vascular injury[26] It is said to result from sudden stretching of a vessel, such as the lateral displacement incident to the exploding force of the missile.[25a] Spasm may result from any obstruction of a vessel[27] and may be due to thrombus formation.[28] Makins[29] stated that arrest of circulation by laceration or embolus may cause constriction proximal and distal to the obstruction. Soon after embolic occlusion of an artery vascular constriction occurs distally.[30]

Despite the foregoing statements, proof of vascular injury does not establish vasospasm as the indisputable cause of ischemia and loss of function of the part ordinarily supplied by the affected vessel. Actually, vascular trauma may produce any of several lesions, each equally capable of causing serious loss of function. Furthermore, primary vasospasm of such degree as to account for such disturbances as those under consideration in this report is so rare that after the first reported case by Kroh, in 1915, there appeared only 42 cases in the literature—none reported by American authors. Montgomery and Ireland,[24a] who collected these cases, brought the total to 44 by adding 2 of their own. In several of the cases they collected the diagnosis is open to doubt because the constriction, if actually present, may have been due to causes other than primary vasospasm. These authors stated the belief that any diagnosis of vasospasm without direct inspection of the vessel must remain doubtful, while Makins[31] cautioned that the degree of structural damage may not be determined by inspection.

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25. (*a*) Cohen, S. M.: Traumatic Arterial Spasm: Hunterian Lecture, Lancet **1**:1-6 (Jan. 1) 1944. (*b*) DaCosta, J. C.: Modern Surgery, ed. 10, Philadelphia, W. B. Saunders Company, 1931, p. 327. (*c*) De Bakey, M.: Traumatic Vasospasm, Bull. U. S. Army M. Dept., February 1944, no. 73, pp. 23-28. (*d*) Holman.[11] (*e*) Learmonth, J. R., in Bailey, H.: Surgery of Modern Warfare, Baltimore, Williams & Wilkins Company, 1940, pp. 310-318. (*f*) Montgomery and Ireland.[24a] (*g*) Scheinker, I. M.: Vasoparalysis of Central Nervous System: Characteristic Vascular Syndrome; Significance in Pathology of Central Nervous System, Arch. Neurol. & Psychiat. **52**:43-57 (July) 1944. (*h*) Trueta, K. J.: Principles and Practice of War Surgery, St. Louis, C. V. Mosby Company, 1943.

26. Carter, B. N., and De Bakey, M. E.: War Wounds of Extremities, Bull. Am. Coll. Surgeons **29**:117-121 (June) 1944.

27. Christopher, F.: Textbook of Surgery, ed. 3, Philadelphia, W. B. Saunders Company, 1942.

28. de Takats, G.: Acute Arterial Occlusions of Extremities, Am. J. Surg. **33**:60-67 (July) 1936.

29. Makins, G. H., cited by Montgomery and Ireland.[24a]

30. Linton, R. R.: Peripheral Arterial Embolism: Discussion of Postembolic Vascular Changes and Their Relation to Restoration of Circulation in Peripheral Embolism, New England J. Med. **224**:189-194 (Jan. 30) 1941.

31. Makins, G. H.: On Gunshot Injuries to the Blood Vessels, New York, William Wood & Company, 1919.

On exploration of the brachial artery in a case of crushing wound of the chest and shoulder, Waters[32] found no evidence of laceration or thrombosis, while the pulseless, constricted vessel presented the distinctive features of vascular spsam. Autopsy, however, revealed occlusion of the artery by loosened flaps of the intima and media.

Manipulation of a vessel at operation may be instrumental in releasing an intravascular clot or in shifting a flap of intima and media in such a manner that circulation is reestablished and the vessel resumes its normal size. Such a process could well lead to the mistaken diagnosis of vasospasm. When constriction of a vessel requires amputation, failure to demonstrate thrombosis, embolism, intimal damage or laceration in the amputated part should not be mistaken as proof of primary vasospasm. Generally, collateral circulation permits saving the damaged segment of vessel in the viable stump; and, as no examination of that segment can be carried out, the true cause of the constriction may never be found.

Before attributing clinical symptoms to segmentary spasm or other local impairment of circulation, one must establish that the volume of blood through the affected vessel together with that available by collateral circulation is inadequate for the functional needs of the tissues concerned. Thus, even absolute proof of primary spasm of the carotid artery is not adequate explanation of cerebral symptoms unless it is also proved that the formation of the circle of Willis is such that the other carotid artery and the vertebral arteries are unable to supply the functional needs of the tissues ordinarily supplied by the affected carotid artery.

Pathologic Changes in Cerebral Embolism.—An embolus lodges where the dimensions of the vessels are inadequate to permit its passage, usually at the origin of a major branch or the bifurcation of an artery. Coagulation products may accumulate until finally an entire segment of the vessel becomes thrombosed. The thrombus may extend distally or proximally and arrest the flow of blood in additional branches or collaterals, thereby affecting the blood flow to previously unaffected tissue. The rapidity and extent of this process are determined by a variety of factors.

Impairment of vascular circulation in the brain leads to an accumulation of carbon dioxide, a particularly active vasodilator.[25g] This condition is further aggravated by the interference with the adequate supply of oxygenated blood to the capillaries and results in increased permeability of the vessel walls. Subsequently, edema and congestion develop. This increase in the area of affected tissue may lead to the appearance of new symptoms. In addition to symptoms referable to the tissue initially affected as a result of retarded circulation, there may develop signs re-

32. Waters, G. B.: Personal communication.

lated to adjacent cerebral tissue, or even to distant structures if the edema should be extensive. Thus, even herniation of the cerebellar tonsils and medullary compression may occur, with fatal results. In occasional instances of extensive impairment of circulation, the patient may survive but suffer degeneration and absorption of a large amount of brain tissue. Less extensive circulatory disturbances in the brain are usually not fatal, though serious signs may result. As with any uncomplicated unilateral cerebral atrophy, passive dilation of the ventricles occurs, and the ventricular system tends to migrate toward the side of the atrophy. The neurologic signs are dependent on the location of the lesion.

Treatment.—The consequences of thrombosis of the carotid artery and secondary cerebral embolism are often so disastrous that prevention is the only satisfactory course. In any injured vessel thrombus formation may occur, and great caution should be exercised to forestall any event which might lead to the detachment of fragments. Immobilization of the head and neck, in order to prevent liberation of an embolus by extravascular influences, may well mean the difference between recovery and grave complications. All manipulations should be delayed as long as possible to reduce the danger inherent in the detachment of fragments. If surgical intervention is required, the vessel should be disturbed as little as possible.

Medication with heparin and dicumarol can be recommended, within certain limitations. In order to be most effective, these drugs must be employed early enough to prevent clotting. They will not dissolve a clot already formed, although they may inhibit its subsequent growth.[33] Heparin and dicumarol are of definite value in reducing postoperative complications incidental to blood clotting, but they are contraindicated under certain conditions.[34] Resistance to heparin occurs in cardiovascular accidents and in Buerger's disease (thromboangiitis obliterans), as well as for three to four days after all major operations.[35] the use of anticoagulants may result in the formation of a hematoma in the wound unless hemostasis is absolute.[36] Learmonth, in recommending heparin in

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33. (*a*) Murray, G. D. W.: Heparin in Surgical Treatment of Blood Vessels, Arch. Surg. **40**:307-325 (Feb.) 1940. (*b*) Pfeiffer, D. B., and Sain, F. D.: Heparin and Dicumarol: Collective Review, Internat. Abstr. Surg. **87**:109-119, 1944; in Surg., Gynec. & Obst., February 1944.

34. Barker, N. W.; Allen, E. V., and Waugh, J. M.: Use of Dicumarol in Prevention of Postoperative Thrombophlebitis and Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. **18**:102-107 (April 7) 1943. Murray.[33a]

35. de Takats, G.: Heparin Tolerance: Test of Clotting Mechanism, Surg., Gynec. & Obst. **77**:31-39 (July) 1943.

36. Learmonth, J. R.: Surgery of Blood Vessels, Edinburgh M. J. **47**:225-240 (April) 1940.

operations involving vascular sutures, commented that the risk of local thrombosis after the third postoperative day is slight, but recommended its use for one or two days longer. Pemberton[37] stated that anticoagulants are definitely indicated in all cases of operation involving important arteries and that they should be prescribed for a period of from ten to twelve days after operation.

For obvious reasons, anticoagulants will prove more effective in planned surgical procedures than in cases of accidental vascular wounds, which by their very nature exist for a time before the rate of coagulation can be retarded. Anticoagulants are not to be recommended unconditionally in all cases of accidental trauma, as they are liable to produce serious oozing or hemorrhage.

It should be emphasized that oxygen and circulatory stimulants often are of considerable benefit in circulatory disturbances of this type. Measures affecting the control or reduction of cerebral edema are important in cases in which the extent of embolic involvement disposes to widespread edema.

SUMMARY AND CONCLUSIONS

Even minor wounds in the vicinity of an artery may result in damage to the intima; thrombosis constitutes the natural response to such involvement.

From 50 to 70 per cent of thromboses of traumatic origin lead to embolism. Minor emboli are fairly well tolerated except in the central nervous system.

In a minority of patients cerebral involvement may occur subsequent to cervical wounds which produce occlusion of the carotid artery, for example, by ligature, or thrombus. In general, however, even after reduction or arrest of blood supply through the carotid arteries has been proved, such cerebral complications cannot be attributed to this cause, unless there is evidence that collateral circulation through the circle of Willis is inadequate to supply the needs of the affected cerebral hemisphere.

Embolism is common, while vascular spasm, with the exception of the secondary and subclinical types, is extremely rare.

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37. Pemberton, J. de J., in discussion on Bigger, I. A.: Treatment of Traumatic Aneurysms and Arteriovenous Fistulas, Arch. Surg. **49**:170-179 (Sept.) 1944.

Cerebral embolism must be taken into consideration in the differential diagnosis of any case in which cerebral signs and a wound in the neck are encountered.

Whenever autopsy reveals the presence of a segmental intravascular clot, the thrombus may be the product of, and superimposed on, an embolus, although the contained embolus often cannot be differentiated, even microscopically, from the enveloping thrombus.

All of the 5 cases reported here were probably instances of cerebral embolism arising from a thrombus of the carotid artery.

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RETINAL, CEREBRAL AND SYSTEMIC ARTERIOSCLEROSIS

A Histopathologic Study

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THE CLOSE anatomic relationship between cerebral and retinal arteries rendered it inevitable, after the introduction of ophthalmoscopy in 1851, that some attempt would be made to correlate disease processes in these arteries. Hirschberg[1] (1882) was the first to attempt this correlation. He noted that patients with retinal arteriosclerosis frequently presented hemiplegias or other signs of cerebral vascular disease. Subsequent clinical studies have shown rather wide discrepancies in the coexistence of cerebral and retinal arteriosclerosis. Moore,[2] in a series of 44 cases of cerebral hemorrhage or thrombosis, found retinal arteriosclerosis of severe degree in 43 per cent and of mild degree in 27 per cent. In a study of 52 cases of retinal arteriosclerosis, he found that cerebral vascular accidents occurred in 44 per cent. Wagener[3] observed retinal arteriosclerosis in only 7 of 27 cases of cerebral arteriosclerosis. Lyle[4] presented in tabular form his observations on 59 patients with cardiovascular-renal disease. From his data, it appears that retinal arteriosclerosis occurred in 9 patients with grossly normal cerebral arteries and in 11 patients with sclerosis of the great vessels at the base of the brain. Despite the wide discrepancy, 70 per cent in Moore's series and 25.9 per cent in Wagner's, the impression has grown clinically that retinal arteriosclerosis indicates cerebral arteriosclerosis.

From the Jefferson Medical College of Philadelphia.

1. Hirschberg, J.: Zur Lehre von der diathetischen Retinitis, Centralbl. f. prakt. Augenh. **6**:327, 1882; cited by Duke-Elder.[12]

2. Moore, R. F.: (*a*) Medical Ophthalmoscopy, Philadelphia, P. Blakiston & Son, 1922; (*b*) Quart. J. Med. **10**:29, 1916.

3. Wagener, H. P.: Observations on Retinal Arteriosclerosis, M. Clin. North America **7**:275, 1923.

4. Lyle, D. J.: The Association Between Retinopathies and Encephalopathies in the Common Cardio-Vascular-Renal Affections, Am. J. Ophth. **34**:402, 1945.

Histologic studies of this problem are few and inadequate. In no series of cases has histologic examination been made of the cerebral arteries, and the interest in ophthalmic vessels has been limited chiefly to the central artery of the retina. Bridgett[5] examined the cerebral vessels grossly and the central retinal artery histologically in 200 cases with autopsy. In 30.4 per cent of 148 cases of sclerosis of the cerebral arteries there was sclerosis of the central retinal artery; in 18.4 per cent of 38 cases with grossly normal cerebral arteries there was sclerosis of the central retinal artery. This series comprised the largest number of cases studied. Verweg[6] examined the retinal vessels in 7 cases with gross sclerosis of the cerebral arteries. In 4 of these cases the retinal vessels were normal, and in 3 there was some degree of sclerosis. Verweg's observations included the smaller arteries and the arterioles of the retina. The observations of Harms, Volhard and Coats are often cited with reference to the problem of retinal and cerebral arteriosclerosis. Harms[7] was concerned only with the central artery of the retina and did not study the cerebral vessels. Volhard's[8] contribution was a review and presented no new data. Coats[9] restricted his observations to a description of the pathologic aspects of retinal vascular disease. Histologic studies on the correlation of retinal and cerebral arteriosclerosis are deficient in the following aspects: (1) They have been concerned chiefly with the central artery of the retina, to the exclusion of other retinal arteries, and (2) cerebral arteries have not been adequately studied.

Despite the wide discrepancies in clinical observations and the lack of conclusive pathologic studies, there had been a definite tendency in teaching to stress and maintain that retinal arteriosclerosis indicates cerebral arteriosclerosis. This concept is commoner among ophthalmologists than among neurologists.

More recent ophthalmologic textbooks hold that retinal arteriosclerosis is an indication of cerebral arteriosclerosis. Parsons[10] stated that

5. Bridgett, C. R.: Sclerosis of Central Artery of Retina, Am. J. Ophth. **9**:725, 1926.

6. Verweg, B. C. deLa F.: Ueber die Arteriosklerosen der Netzhaut und ihre Bedeutung für die Genese der Retinitis albuminurica, Klin. Monatsbl. f. Augenh. **79**:148, 1927.

7. Harms, C.: Hemorrhage Retinitis in Consequence of Disease of the Central Artery of the Retina, Arch. Ophth. **34**:202, 1905.

8. Volhard: Die Pathogenese der Retinitis albuminurica, Zentralbl. f. d. ges. Ophth. **21**:129, 1929.

9. Coats, G.: A Case of Thrombosis of the Central Vein: Pathological Aspects, Tr. Ophth. Soc. U. Kingdom **24**:165, 1904; **33**:37, 1913.

10. Parsons, J. H.: Diseases of the Eye, ed. 7, New York, The Macmillan Company, 1934.

retinal arteriosclerosis may be the first evidence of arteriosclerosis, particularly of disease of the cerebral vessels. On the basis of the previously cited work of Moore,[2b] he concluded that cerebral arteriosclerosis is invariably associated with retinal arteriosclerosis. May[11] stated that arteriosclerotic retinopathy accompanies generalized arteriosclerosis and that the arteriosclerosis of the retinal vessels indicates similar changes elsewhere, especially in the brain. Duke-Elder,[12] after citing freely from the literature and noting the wide discrepancies, stated that on the whole a striking relation exists between the vessels of the eye and those of the brain. Friedenwald[13] concluded that in sclerosis of the arterioles the vessels of the choroid and those of the retina are usually involved similarly, whereas in atheromatous degeneration of larger arteries there are frequently arteriosclerotic changes in the eyes.

Neurologic texts do not subscribe as readily to the concept that retinal arteriosclerosis indicates cerebral arteriosclerosis. Oppenheim[14] cited Geis to the effect that retinal arteriosclerosis may warn of impending cerebral vascular accidents. Grinker and Levy[15] stated merely that cerebral arteriosclerosis may be mirrored by arteriosclerosis of the retinal vessels. Wilson[16] expressed the opinion that retinal angiosclerosis is a feature of advanced cerebral arteriosclerosis, but a feature subject to wide variation. Alpers[17] concluded that retinal arteriosclerosis is a constant feature of cerebral thrombosis and a frequent, but inconstant, accompaniment of cerebral hemorrhage. Some neurologic textbooks (Nielsen,[18] Bing and Haymaker,[19] Jelliffe and White[20] and Brain[21]) make

11. May, C. H.: Manual of Diseases of the Eye for Students and General Practitioners, ed. 15, Philadelphia, William Wood & Company, 1937.

12. Duke-Elder, W. S.: Text-Book of Ophthalmology, London, Henry Kimpton, 1940.

13. Friedenwald, J. S.: Retinal and Choroidal Arteriosclerosis, in Ridley, F., and Sorsby, A.: Modern Trends in Ophthalmology, London, Butterworth & Co., 1940.

14. Oppenheim, H.: Lehrbuch der Nervenkrankheiten für Ärzte und Studierende, Berlin, S. Karger, 1913.

15. Grinker, R. R., and Levy, N. A.: Neurology, ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1943.

16. Wilson, S. A. K.: Neurology, Baltimore, William Wood & Company, 1940.

17. Alpers, B. J.: Clinical Neurology, Philadelphia, F. A. Davis Company, 1945.

18. Nielsen, J. M.: A Textbook of Clinical Neurology, New York, Paul B. Hoeber, Inc., 1941.

19. Bing, R., and Haymaker, W.: A Textbook of Nervous Diseases, St. Louis, C. V. Mosby Company, 1939.

20. Jelliffe, S. E., and White, W. A.: Diseases of the Nervous System: A Textbook of Neurology and Psychiatry, ed. 6, Philadelphia, Lea & Febiger, 1935,

no reference to the possible correlation of retinal and cerebral arteriosclerosis. Textbooks of neuropathology do not mention the subject.

The clinical views may then be summarized as follows: From the ophthalmologic standpoint, retinal arteriosclerosis is considered evidence of cerebral arteriosclerosis, and this despite a respectable percentage of cases with sclerosis only of the retinal or the cerebral vessels. From the neurologic viewpoint, convictions are not so strongly in favor of a correlation between cerebral and retinal arteriosclerosis. Neuropathologists have not concerned themselves with this problem. The pathologic evidence cited reveals that only one long series of cases has been studied, and in this series the only ophthalmic vessel studied was the central artery of the retina, whereas the cerebral vessels were not studied histologically. Since clinical evaluations have been inconclusive and pathologic studies have not been adequate, the following studies were made.

MATERIAL AND METHODS

Histologic study of the retinal and cerebral vessels was made in 100 adults on whom autopsy was performed. For this study, blocks were taken in each case from the following structures: the eye, with choroid and retina; the basilar artery; the cerebral cortex, including the leptomeninges, and the globus pallidus, putamen and internal capsule. All blocks were embedded in paraffin, and sections were stained with hematoxylin and eosin and with Van Gieson's elastica stain. In some cases Masson's trichrome stain was also employed. Both choroidal and retinal arteries were studied, since choroidal arteries may be seen on ophthalmoscopic examination, their visibility depending on the amount of pigmentation present.

The block of basilar artery was taken from the superior portion of the artery extending up to the bifurcation into the two posterior cerebral arteries. This site was chosen to avoid the lower portion of the basilar artery, which in some cases is similar in architecture to arteries elsewhere in the body, whereas the upper portion always has the characteristics of a cerebral artery. The choice of blocks permitted sampling throughout the distribution of various arteries, as well as a gradient in size of arteries. The block of cortex, taken from the medial aspect, included branches of the anterior cerebral artery, and the block of globus pallidus, branches from the middle cerebral artery. The basilar artery is, of course, one of the larger cerebral vessels, and the meningeal vessels are in the classification of smaller arteries, the cortical vessels and those of the globus pallidus allowing a range from small arteries to precapillary arterioles.

In addition to the chorioretinal arteries and the aforementioned cerebral arteries, certain arteries in the general systemic circulation were studied histologically. These included the aorta; the coronary arteries; the parenchymal arteries of the lung, adrenal glands, pancreas, spleen and liver; the renal arteries; the larger arteries of the renal parenchyma, and the glomerular arteries.

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21. Brain, R.: Diseases of the Nervous System, ed. 2, London, Oxford University Press, 1940.

RESULTS

In 14 of the 100 cases studied, there was no histologic evidence of arteriosclerosis in either the retinal or the cerebral blood vessels. In the remaining 86 cases, arteriosclerosis of the various cerebral and/or retinal

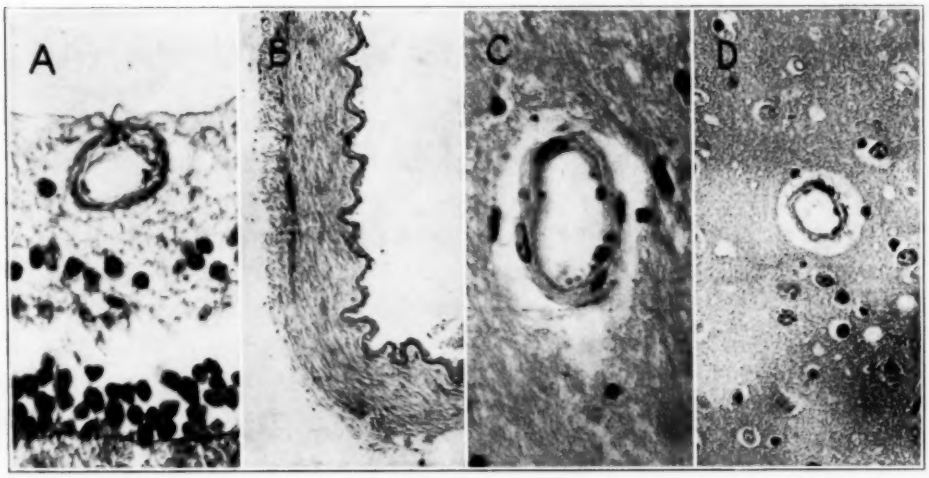

Fig. 1.—Case with retinal arteriosclerosis and normal cerebral arteries. *A* shows a small retinal artery with intimal proliferation and splitting of the elastica, × 395; *B*, normal basilar artery, × 87; *C*, normal small artery of cerebral cortex, × 395; *D*, normal arteriole of basal ganglia, × 395. All sections were stained with hematoxylin and eosin.

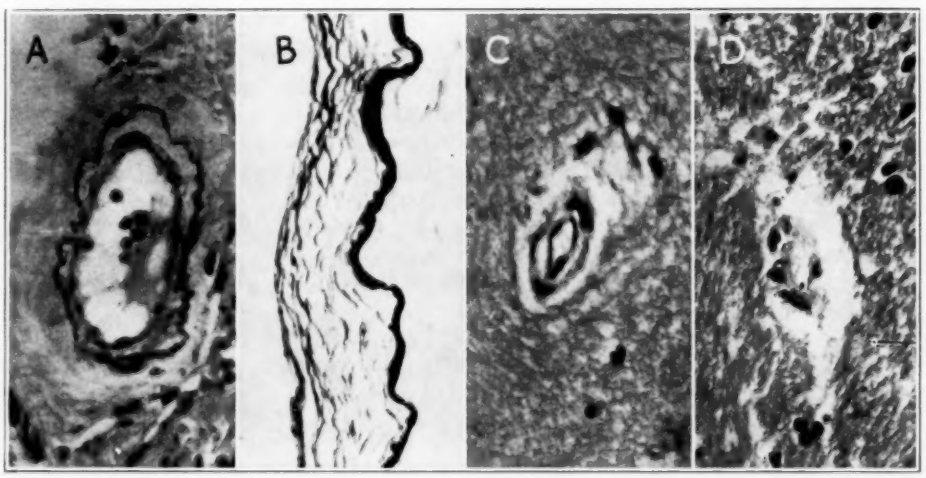

Fig. 2.—Case with arteriosclerosis of choroidal and cerebral vessels. *A*, choroidal artery with intimal proliferation and hyalinization of media; hematoxylin and eosin stain, × 368. *B*, wall of basilar artery, with intimal proliferation and splitting of elastica; Van Gieson's elastica stain, × 165. *C*, arteriole of cerebral cortex, showing hyalinization and thickening of the media; hematoxylin and eosin stain, × 327. *D*, arteriole of basal ganglia, with thickening and hyalinization; hematoxylin and eosin stain, × 327.

blood vessels was indicated by degenerative changes in the constituent coats of the vessel walls (figs. 1 to 4). In the basilar artery the features of arteriosclerosis consisted in one or a combination of the following changes: (1) proliferation and degeneration of the intima; (2) hy-

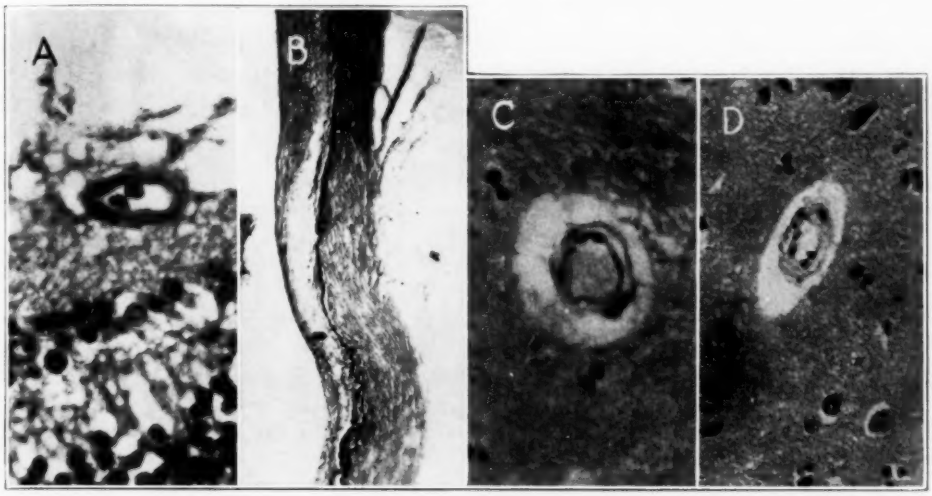

Fig. 3.—Case with normal retinal vessels and sclerosis of cerebral vessels. *A*, small artery of retina, normal; hematoxylin and eosin, × 342. *B*, basilar artery, with splitting of elastica and proliferation of intima; Van Gieson's elastica stain, × 132. *C*, arteriole of cerebral cortex, with thickening and hyalinization of media; hematoxylin and eosin stain, × 385. *D*, arteriole of basal ganglia, with thickening and hyalinization of media; hematoxylin and eosin stain, × 175.

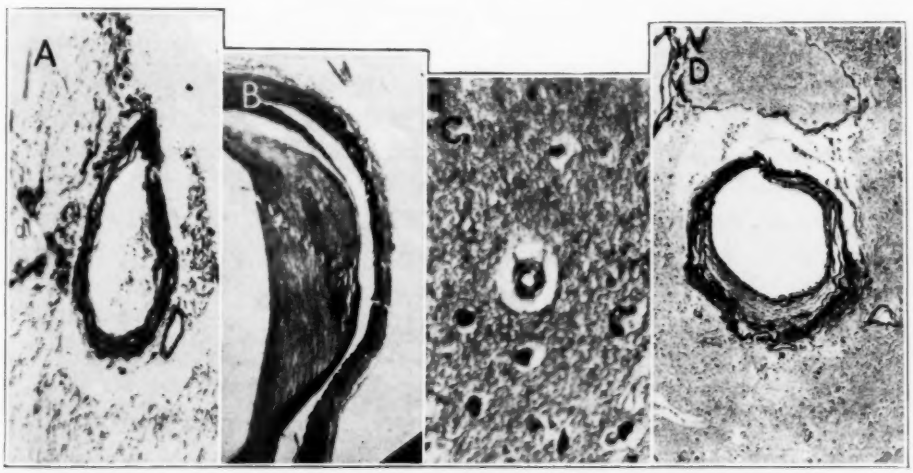

Fig. 4.—Case with normal retinal vessels and sclerosis of cerebral vessels. *A*, normal central artery of retina and a branch; hematoxylin and eosin stain, × 180. *B*, basilar artery with intimal proliferation, fraying of elastica and medial degeneration; hematoxylin and eosin stain, × 135. *C*, arteriole of cerebral cortex, with hyalinization of media; hematoxylin and eosin stain, × 180. *D*, large artery of basal ganglia, with intimal proliferation and splitting of elastica; Van Gieson's elastica stain, × 180.

alinization, splitting or fraying of the elastica, and (3) hyalinization and degeneration of the media. Sclerosis of the larger cortical vessels was indicated by hyalinization or degeneration of the media, with or without alterations of the elastica. Smaller cortical vessels, such as arterioles or smaller arteries, when sclerotic, became hyalinized and thickened. The alterations of the vessels of the basal ganglia were similar in type to those of the cortical vessels. In addition, pseudocalcification occurred in some vessels of the lenticular nucleus. Arteries of the meninges over the vertex and in the cerebral sulci were studied in each case. In only 2 cases had the meningeal vessels undergone sclerotic changes. Sclerosis of the choroidal and retinal arteries consisted of alterations in the central artery of the retina similar to those previously described in larger cortical arteries and in the arteries of the basal ganglia. In the smaller retinal and choroidal arteries there occurred hyalinization and thickening of the media and hyalinization of the elastica, with only occasional splitting of the elastic membrane. The choroidal and retinal vessels differ somewhat from the cerebral vessels in that the elastic tissue is not banded together as compactly in an internal elastic membrane. This tendency to diffusion of elastic tissue through the media renders evaluation of sclerotic alterations of the elastica somewhat more difficult than in cerebral vessels. However, definite hyalinization and fraying of the elastica are rather readily observed. Intimal proliferation occurred in choroidal and retinal arteries. Whenever the choroidal vessels were sclerosed, the retinal vessels had likewise undergone degenerative changes, but these alterations were not always commensurate in degree. When a disparity occurred in the degree of involvement, the choroidal vessels were more extensively affected.

In 86 cases arteriosclerosis occurred in one or more of the groups of vessels studied. Sclerosis occurred (independently) in either the cerebral or the retinal arteries (figs. 2 to 4). In 14 cases there was no histologic evidence of retinal or cerebral arteriosclerosis. Retinal arteriosclerosis was observed without cerebral arteriosclerosis in 6 cases. In 35 cases both cerebral and retinal arteriosclerosis occurred. Therefore arteriosclerosis of some cerebral vessels occurred in approximately 6 of 7 cases of retinal arteriosclerosis. However, cerebral arteriosclerosis occurred without retinal arteriosclerosis in 45 cases, indicating that retinal arteriosclerosis occurred in only 7 of 16 cases of cerebral arteriosclerosis. Retinal arteriosclerosis occurs far more commonly with than independent of cerebral arteriosclerosis, but cerebral arteriosclerosis occurs slightly more commonly independent of than with retinal arteriosclerosis (fig. 5). The group of 86 cases of arteriosclerosis was subdivided according to the distribution of the retinal and the cerebral arteriosclerosis. These subgroups are presented in figure 6. By rearrangement of subgroups, it

was possible to determine the relation between sclerosis of the retinal arteries and sclerosis of any of the cerebral vessels studied: basilar artery; cortical and meningeal arteries, and arteries of the basal ganglia. The only positive correlation found was between retinal arteriosclerosis and sclerosis of the basilar artery (fig. 7,*I*). Sclerosis of the retinal

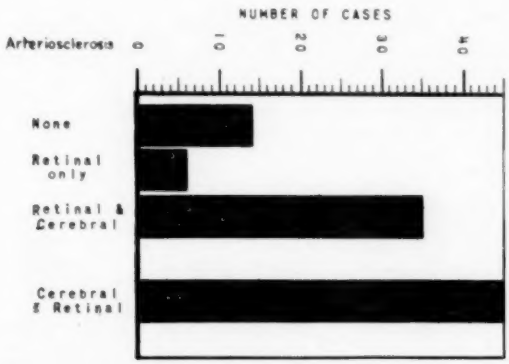

Fig. 5.—Incidence and distribution of arteriosclerosis in 100 cases. *None* refers to cases with normal retinal and cerebral arteries; *Retinal only,* to cases with histologic evidence of retinal arteriosclerosis but with normal cerebral vessels; *Retinal & cerebral,* to cases with histologic evidence of sclerosis of retinal arteries and of all, or some, of the cerebral vessels studied; *Cerebral & Retinal,* cases with sclerosis of some or all of the cerebral vessels studied but with normal retinal arteries.

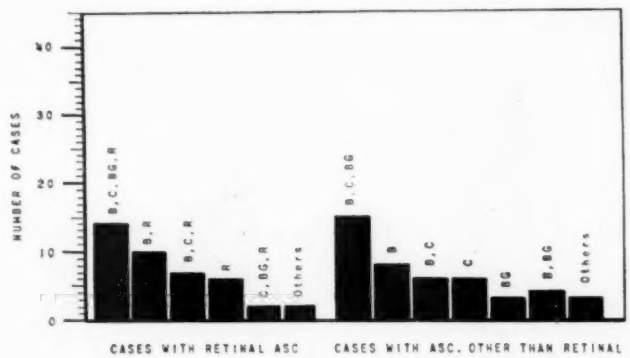

Fig. 6.—Incidence of arteriosclerosis in the various vessels studied. In this, and in subsequent figures, *B* refers to basilar artery; *C* to cortical arteries; *BG,* to arteries of basal ganglia, and *R* to retinal arteries. *Others* include combinations occurring infrequently, such as sclerosis of the meningeal vessels. *ASC* stands for "arteriosclerosis."

arteries, but not of the basilar artery, occurred in 8 cases, and sclerosis of both retinal and basilar arteries occurred in 33 cases. Thus, sclerosis of the basilar artery occurred in approximately 4 of 5 cases with retinal arteriosclerosis. Sclerosis of the basilar artery without retinal arteriosclerosis was present in 35 cases. Sclerosis of the basilar artery was at least

as common in the absence of retinal arteriosclerosis as in its presence. In 10 cases with arteriosclerosis neither the basilar artery nor the retinal vessels showed sclerotic changes.

Arteriosclerosis of the meningeal vessels was so uncommon as to be negligible, as it occurred in only 2 cases. Obviously, no correlation could be drawn from this observation.

Sclerosis of the retinal arteries without involvement of the arteries of the basal ganglia occurred in 24 cases, whereas both the retinal ar-

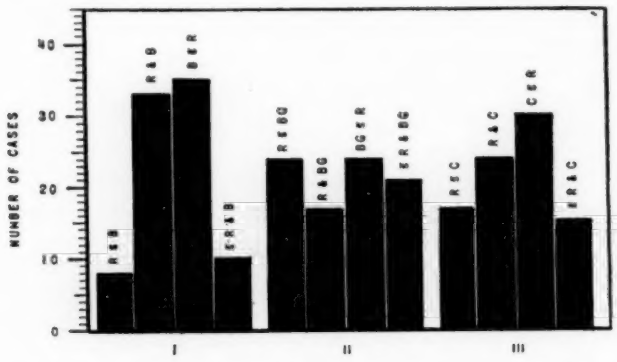

Fig. 7.—Correlations of retinal arteriosclerosis with sclerosis of the various cerebral vessels studied. Letters have same meaning as in figure 6.

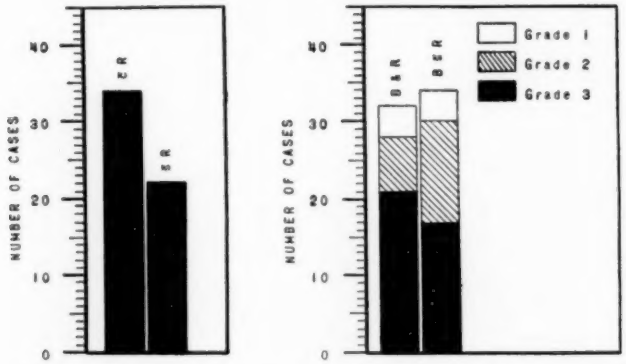

Fig. 8.—*A*, correlation of retinal arteriosclerosis with sclerosis of arteries in more than one cerebral area studied. *B*, correlation of degree of sclerosis of basilar artery with presence of retinal arteriosclerosis. Grades of sclerosis of basilar artery are explained in text.

teries and the arteries of the basal ganglia were sclerosed in 17 cases (fig. 7,*II*). In 24 cases sclerosis occurred in the arteries of the basal ganglia but not in the retinal arteries. Therefore, the arteries of the basal ganglia were sclerosed in less than one-half the cases of retinal arteriosclerosis, and the retinal arteries were sclerosed in less than one-half the cases with sclerosis of the arteries of the basal ganglia.

In 17 cases the retinal, but not the cortical, arteries gave evidence of arteriosclerosis, whereas in 24 cases both retinal and cortical arteries and arterioles were sclerosed. In 30 cases the cortical, but not the retinal, arteries had undergone sclerotic alterations. Obviously, no significant opinion can be derived from the retinal arteries regarding the cortical arteries and arterioles.

The results of these comparisons are summarized as follows: Retinal arteriosclerosis occurs in combination with cerebral arteriosclerosis about six times as frequently as it occurs without cerebral arteriosclerosis, but sclerosis of the cerebral vessels occurs as frequently in the absence as in the presence of retinal arteriosclerosis. The distribution of cerebral arteriosclerosis in this series shows that retinal arteriosclerosis indicates a 4:1 possibility that the basilar artery is sclerosed, but gives no definite indication that the arteries of the cortex, basal ganglia or meninges are

TABLE 1.—*Comparison of Incidence of Retinal and Cerebral Arteriosclerosis According to Age Groups*

Age Group, Yr.	Total No. of Cases	Retinal and Cerebral Arterio-sclerosis	Cerebral Arterio-sclerosis Only	Retinal Arterio-sclerosis Only	Neither Retinal nor Cerebral Arterio-sclerosis
15-24	2	1	1	....	....
25-34	5	1	1	1	2
35-44	10	4	5	....	1
45-54	21	6	8	2	5
55-64	26	7	10	3	6
65-74	28	13	15	....	....
75+	8	3	5	....	....
Total #	100	35	45	6	14

involved. The basilar artery and the arteries of the cortex and of the basal ganglia were more often sclerosed without than with involvement of the retinal artery.

The possibility was considered that this material might be weighed by either of the following factors: (1) a large number of cases with a minimal number of lesions or (2) a large proportion of cases with mild or early arteriosclerosis. To test the first possibility, the incidence of retinal arteriosclerosis was determined in cases with degenerative changes in two or more of the groups of vessels studied (fig. 8). Sixty cases presented degenerative changes in two or more of the groups of vessels studied. In 33 of these 60 cases the retinal arteries were sclerosed, while in 27 cases the retinal vessels were normal. Figure 8 also presents an analysis of the degree of sclerosis of the basilar artery in relation to the incidence of retinal arteriosclerosis. Sclerosis of the basilar artery was graded as 1, 2 and 3. This grading depended on the number of struc-

tures in the wall of the vessel involved in the process. If intimal proliferation, splitting of the elastica or degeneration of the media occurred, the sclerosis was classed as grade 1. A combination of any two of these changes comprised grade 2, and that of all three, grade 3. Of the 32 cases of basilar and retinal arteriosclerosis, 20 presented sclerosis of the basilar artery of grade 3, and 8, of grade 2. Of the 31 cases of basilar sclerosis without retinal arteriosclerosis, 16 presented sclerosis of grade 3, and 12, of grade 2.

The distribution of the arteriosclerotic process was also studied with reference to the ages of the patients. Table 1 presents these data. While arteriosclerosis of both retinal and cerebral vessels was uniformly en-

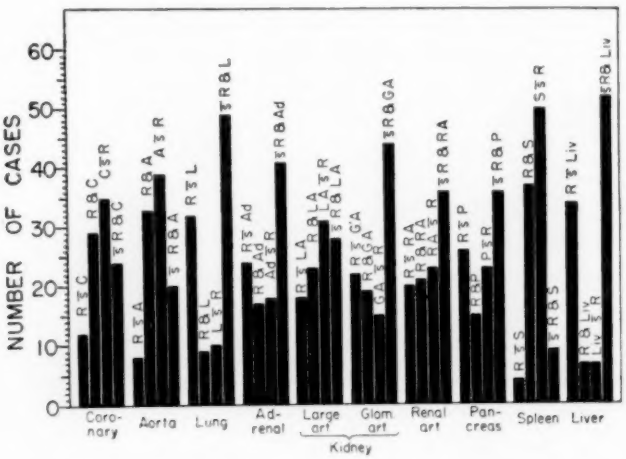

Fig. 9.—Incidence of retinal and systemic arteriosclerosis. *R* indicates retinal arteriosclerosis. Sclerosis of other vessels is indicated as follows: *A*, aorta; *LA*, large arteries of kidney; *GA*, glomerular arteries of kidney; *RA* renal artery, and *L, Ad, P, S* and *Liv*, arteries of the lung, adrenal gland, pancreas, spleen and liver, respectively.

countered after the age of 64, in all the age decades studied cerebral arteriosclerosis was at least as common without as with retinal arteriosclerosis. This persistent trend in each age group indicates that the compilations under the various distributions of arteriosclerosis are not weighted by disproportionate sampling within a given age group.

While this report is primarily concerned with arteriosclerosis of the cerebral and retinal vessels, it is not feasible to divorce arteriosclerosis of these structures from arteriosclerosis elsewhere in the body. Therefore, the correlations were determined for retinal arteriosclerosis and sclerosis of the following vessels: the aorta; the coronary arteries; the renal artery; the larger arteries within the renal parenchyma; the glomerular arteries, and small arteries of the lungs, spleen, liver and pancreas. These correlations are presented in figure 9. Sclerosis of the

retinal vessels more commonly occurred with than without sclerosis of the aorta, coronary arteries and splenic arteries, but sclerosis of the vessels last mentioned occurred more commonly in the absence of than in conjunction with retinal arteriosclerosis. Indeed, sclerosis of all the vessels studied occurred more frequently without than with retinal arteriosclerosis, except for sclerosis of the glomerular arteries. However, retinal arteriosclerosis occurred more frequently in the absence of than with glomerular arteriosclerosis.

Table 2 presents the compilations in the various age groups for retinal, cerebral and systemic arteriosclerosis. As shown also in table 1, there is a persistent trend toward a higher incidence of arteriosclerosis in the absence of retinal arteriosclerosis.

While not germane to the problem of retinal and cerebral arteriosclerosis, the data at hand permitted a ready analysis of the incidence of

TABLE 2.—*Comparison of Incidence of Retinal, Cerebral and General Systemic Arteriosclerosis in Different Age Groups*

Age Group	No. of Cases	Cerebral and Systemic Arterio-sclerosis Only	Retinal, Cerebral and Systemic Arterio-sclerosis	Retinal and Cerebral Arterio-sclerosis Only	Retinal and Systemic Arterio-sclerosis Only	Systemic Arterio-sclerosis Only	Cerebral Arterio-sclerosis Only	Retinal Arterio-sclerosis Only	No Arterio-sclerosis
15-24	2	1	1	....	....	....	....	....	....
25-34	5	....	1	....	1	2	1	....	....
35-44	10	4	4	....	....	....	1	....	1
45-54	21	7	6	....	1	5	1	1	....
55-64	26	10	6	1	1	5	....	2	1
65-74	28	14	13	....	....	....	1	....	....
75-	8	5	3	....	....	....	....	....	....
Totals	100	41	34	1	3	12	4	3	2

basilar and cortical arteriosclerosis and of sclerosis of the basilar artery and the arteries of the basal ganglia. This analysis is presented in figure 10. The basilar artery was sclerosed without arteriosclerosis of the cerebral cortex in 23 cases; both basilar and cortical vessels were sclerosed in 45 cases; cortical vessels but not the basilar artery were sclerosed in 9 cases, and neither basilar nor cortical arteries were sclerosed in 9 cases. The basilar artery, but not the arteries of the basal ganglia, was sclerosed in 30 bases; both the basilar artery and the arteries of the basal ganglia, in 33 cases; the arteries of the basal ganglia, but not the basilar artery, in 6 cases, and the vessels in neither area, in 17 cases.

In the course of these histologic studies, so-called pseudosclerosis of the arteries of the lenticular nucleus was observed in 11 cases. In 3 of the 11 cases no arteriosclerosis occurred, either in the lenticular nucleus or elsewhere, and of the remaining 8 cases, with pseudosclerosis and

arteriosclerosis, the arteries of the basal ganglia were sclerotic in only 4 cases.

COMMENT

Largely on the basis of clinical impressions, retinal arteriosclerosis is considered evidence of cerebral arteriosclerosis. However, clinical observations have not been uniform in substantiating this impression, and histologic studies of the problem have been inadequate and oriented almost exclusively from an ophthalmologic point of view, with consequent overemphasis on the retinal arteries and virtual exclusion of adequate study of the cerebral vessels. The present studies were made to determine whether any basis exists for assuming the state of the cerebral

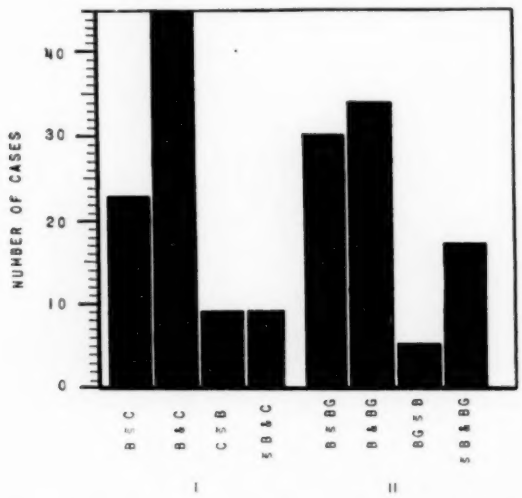

Fig. 10.—Correlation of sclerosis of basilar artery with sclerosis of arteries of cortex and basal ganglia. Letters have same meaning as in figure 5.

arteries from the condition of the retinal arteries. Of 100 cases with autopsy, cerebral and/or retinal arteriosclerosis was encountered in 86. The incidence of arteriosclerosis was determined for the arteries of the retina, cerebral cortex, basal ganglia and meninges and for the basilar artery. In slightly less than one-half the cases of cerebral arteriosclerosis were the retinal arteries degenerated, and therefore the absence of retinal arteriosclerosis is not an indication that cerebral arteriosclerosis is not present. When the series of cases with cerebral arteriosclerosis was subdivided according to the groups of vessels studied, the same situation obtained; i.e., the absence of retinal arteriosclerosis is not assurance that there is not arteriosclerosis of the basilar artery or the arteries of the cerebral cortex or basal ganglia.

While normal retinal arteries yield no information as to the state of the cerebral vessels, the presence of retinal arteriosclerosis offers a 6:1 probability that there is cerebral arteriosclerosis. On analysis of correlations in subgroups, it is evident that this strong probability is largely absorbed by the correlation between retinal arteriosclerosis and sclerosis of the basilar artery. Retinal arteriosclerosis offers a 4:1 probability that the basilar artery is sclerosed, but there is no significant correlation between degenerative changes of the retinal arteries and those of the cortex or the basal ganglia. These findings gather still more importance when considered with the neurologic conditions associated with cerebral arteriosclerosis. Degenerative changes in the great vessels at the base of the brain are almost routine observations in autopsies on adults in late life (Aring[22]), and are frequently symptomless. Aneurysms of these vessels seldom have their genesis in degenerative changes. Alteration in the visual fields due to pressure on the optic nerve by a tortuous, arteriosclerotic internal carotid artery is rare. For these reasons, the present neuropathologic studies were extended to include vessels of the cortex and basal ganglia. The cortical vessels of the frontal lobe were chosen so as to include the regions commonly undergoing atrophy due to arteriolosclerosis. Cerebral vascular accidents seldom arise directly from lesions of the great vessels of the base. Cerebral hemorrhages are within the substance of the hemisphere, and hence are not due to rupture of the main trunks of the great cerebral vessels. Cerebral thromboses almost invariably indicate by their location that only a branch of the larger vessels has been occluded. Both cerebral hemorrhage and cerebral thrombosis are most frequent in the region of the internal capsule and the basal ganglia—the area which Wilson[16] described as the "danger zone." The complex blood supply of this area has recently been described by Alexander.[23] The sections of the basal ganglia studied for this paper included the globus pallidus, the internal capsule and the putamen so that an adequate evaluation could be made of the state of the arteries in this "danger zone." The importance of retinal vascular disease as an indication of cerebral vascular disease is rendered even less reliable by the inability to correlate retinal arteriosclerosis with degenerative changes in those cerebral vessels at fault in the commoner arteriosclerotic diseases of the brain.

The incidence of retinal arteriosclerosis as compared with noncerebral, systemic arteriosclerosis in this series was in many respects similar to the correlation between retinal and cerebral arteriosclerosis. In 90 of the

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22. Aring, C. D.: Vascular Diseases of the Nervous System, Brain **68**:28, 1945.

23. Alexander, L.: The Vascular Supply of the Strio-Pallidum, A. Research Nerv. Ment. Dis., Proc. (1940) **21**:77, 1942.

100 cases systemic arteriosclerosis was present, but retinal arteriosclerosis occurred in only 37 of the 90 cases. Retinal arteriosclerosis may be considered somewhat indicative of sclerosis of the aorta, coronary arteries or splenic arteries, but the absence of retinal arteriosclerosis is not indicative of a normal condition of these arteries.

The conclusions derived from our results are not erroneous on the basis of sampling cases of early arteriosclerosis. The relative infrequency of retinal arteriosclerosis in cases of cerebral arteriosclerosis was found to obtain only when the cases with arteriosclerosis of two or more of the groups of vessels were studied. Likewise, analysis of the relation of the degree of sclerosis in the basilar arteries to the incidence of retinal arteriosclerosis reveals that no significant discrepancy occurs in the various groups. For these reasons, possible weighting of this material with early cases by either distribution or lesions or stage of the arteriosclerotic process did not produce erroneous results.

Retinal arteriosclerosis as seen ophthalmoscopically and histologically cannot be considered necessarily the same. Wilson[16] suggested that alterations of the retinal blood vessels as observed ophthalmoscopically, and generally construed as arteriosclerotic in type, need not indicate histologic evidence of retinal arteriosclerosis, and may in large part depend on physiologic phenomena. This view has gained further support from the observations of Rodin[24] in a case of pheochromocytoma of the adrenal gland with hypertensive retinopathy. After removal of the tumor, the exudate disappeared, the retinal vessels became slightly less tortuous and arteriovenous nicking decreased.

The histologic studies here reported indicate that cerebral arteriosclerosis is as prevalent without as with retinal arteriosclerosis and that retinal arteriosclerosis indicates sclerosis of the basilar artery, but not of the parenchymal vessels. This suggests tthat it is unwise to rely on the presence or absence of retinal arteriosclerosis in the differential diagnosis of cerebral lesions. The possibility that the ophthalmoscopic picture of retinal arteriosclerosis may be dependent on factors other than pathologic changes within the retinal vessels strengthens the validity of this suggestion and recalls the opinion expressed by Taylor,[25] namely,

24. Rodin, F. H.: Hypertensive Retinopathy Associated with Adrenal Medullary Tumor: Pheochromocytoma, Arch. Ophth. **34**:402 (Nov.-Dec.) 1945.

25. Taylor, J.: Vascular and Other Retinal Changes Associated with Generalized Disease, Tr. Ophth. Soc. U. Kingdom **33**:1, 1913.

that in evaluating the problem of arteriosclerosis one cannot rely on the appearance of the retinal vessels but must depend on evidence of other visceral changes.

There are no studies of similar scope with which our results can be compared. Bridgett studied only the central artery of the retina histologically and the cerebral arteries grossly. He reported that the central artery was normal in 43.9 per cent of the cases with sclerosis of the cerebral arteries and in 68.4 per cent of cases with normal cerebral arteries. The studies of the central artery were made in the substance of the optic nerve, and the observations were limited to the one artery. Moreover, histologic studies on the central artery are more difficult to translate into clinical concepts, since the central artery is not prominent on ophthalmoscopic examination. Moreover, a plaque of the artery might easily be missed on a set of sections through the nerve head, whereas sections of the retina and choroid present the possibility of observing numerous arteries. Nevertheless, Bridgett's observations, limited in their scope as they are, suggested that retinal arteriosclerosis cannot be considered a necessary counterpart of cerebral arteriosclerosis. Rearrangement of his figures shows that sclerosis of the basilar vessels occurs without sclerosis of the retinal artery in 43.9 per cent, without sclerosis of the basilar and retinal arteries in 56.1 per cent and without sclerosis of the central artery of the retina only in 31.6 per cent.

The relative unimportance of sclerosis of the great vessels at the base of the brain has recently been emphasized by Aring.[22] The inability to correlate sclerosis of the arteries either of the cerebral cortex or of the basal ganglia with sclerosis of the basilar artery is in accordance with this view, and further detracts from the significance of retinal arteriosclerosis, for the only correlation which could be drawn from the incidence of retinal arteriosclerosis was that it indicated the possibility of sclerosis of the basilar artery.

Pseudosclerosis of the vessels of the basal ganglia consists in the deposition of a substance with much of the staining qualities of calcium. Deposition occurs in the media and adventitia of the arteries and also in the walls of capillaries and veins. Jakob[26] reviewed this subject and pointed out that the process has nothing in common with arteriosclerosis.

26. Jakob, A.: Anatomie und Histologie des Grosshirns, Leipzig, Franz Deuticke, 1927.

The presence of pseudosclerosis without arteriosclerosis in this series is further confirmation of this statement.

SUMMARY

The presence of retinal arteriosclerosis indicates the possibility of cerebral arteriosclerosis, involving the basilar artery, but gives no indication of the state of the arteries and arterioles of the cerebral cortex, meninges and basal ganglia. The absence of retinal arteriosclerosis is not an indication of the absence of cerebral arteriosclerosis, considered in terms either of the group or of any of the specific vessels studied.

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ELECTROMYOGRAPHIC STUDY OF DEFECTS OF NEUROMUSCULAR TRANSMISSION IN HUMAN POLIOMYELITIS

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POLIOMYELITIS is generally considered to be primarily a disease of the motor neurons of the anterior horns of the spinal cord. The loss of muscle substance and of power which often follows the acute stage of this virus infection are explained on the basis of atrophy and fibrosis resulting from denervation, similar to the pathologic changes observed after section of a peripheral nerve or damage to a ventral root (O'Leary, Heinbecker and Bishop[1]).

This study gives evidence that destruction of the cell bodies of somatic motor neurons is not the only alteration of the neuromuscular apparatus in poliomyelitis. Inability to maintain muscle tension during even brief movement or during brief repetitive stimulation of the motor nerve has been demonstrated in patients examined long after subsidence of the acute infection. This abnormal behavior has been shown to be due to a deficiency at the neuromyal junction. Current concepts of the pathologic process in poliomyelitis, therefore, should be broadened to include the abnormalities of peripheral structures responsible for transmission of the nerve impulse to the striated muscle.

PRESENT INVESTIGATION

MATERIAL AND METHODS

Twenty-two patients with chronic poliomyelitis, 12 male and 10 female, from 7 to 17 years of age, were examined electromyographically. The onset of symptoms of acute poliomyelitis had occurred 2.8 to 11.4 years previously.

The patients sat or lay on a cot in a comfortable position in an electrically shielded room. Condenser discharges, controlled by a gas tetrode and delivered to the electrodes through an isolating transformer, were applied percutaneously to the nerves supplying the muscles of the forearm, hand, leg and foot (Harvey

This study was aided by a grant from the National Foundation for Infantile Paralysis, Inc.

From the Department of Physical Medicine and the Johnson Research Foundation, University of Pennsylvania.

1. O'Leary, J. L.; Heinbecker, P., and Bishop, G. H.: Nerve Degeneration in Poliomyelitis: Physiologic and Histologic Studies on the Roots and Nerves Supplying Paralyzed Extremities of Monkeys During Acute Poliomyelitis, Arch. Neurol. & Psychiat. **28**:272-298 (Aug.) 1932.

TABLE 1.—*Maximal Muscle Action Potentials for Children*

		A. Poliomyelitis				B. Normal[4]		
Nerve Stimulated	Muscles Recorded	Years Since Onset of Symptoms	Age, Years	Sex	Potential, Millivolts*	Age, Years	Sex	Potential, Millivolts*
Tibial	**Leg**	4.5	16	M	12.3	10	M	18.9
		8.7	17	F	10.0	16	F	17.9
		5.0	15	F	9.1	10	M	17.7
		5.0	15	F	9.1	10	M	17.0
		2.8	12	M	4.9	14	F	15.4
		6.8	10	F	2.1	16	F	13.7
		6.7	8	M	0.9	13	F	9.8
		6.7	8	M	0.5			
		6.5	9	F	0.5			
		10.0	12	F	0.5			
		11.4	13	M	0.4			
		4.0	17	M	0.4			
		4.8	16	F	0.2			
		4.7	7	M	0			
		4.5	16	M	0			
		3.5	16	F	0			
		4.0	17	M	0			
		11.4	13	M	0			
		13.5	14	F	0			
				Average	2.7			15.7
	Sole of foot	5.0	15	F	13.0	11	M	18.2
		6.7	8	M	12.5	10	M	14.3
		6.8	14	F	12.5	14	F	13.3
		6.7	8	M	11.3	15	F	12.9
		2.8	12	M	10.1	10	M	12.2
		4.7	7	M	9.4	16	F	11.4
		5.0	15	F	7.5	10	M	11.1
		10.0	12	F	4.9	10	M	8.8
		10.0	12	F	4.2	14	F	7.2
		6.5	9	F	3.8	9	F	5.1
		4.5	16	M	2.6			
		4.8	16	F	1.6			
		6.8	10	F	0.5			
		4.5	16	M	0.3			
		5.4	7	M	0.2			
		3.5	16	F	0			
		11.4	13	M	0			
		13.5	14	F	0			
		6.0	17	F	0			
				Average	5.0			11.5
Common peroneal	Leg	4.6	17	F	5.4	14	F	8.1
		5.0	15	F	4.2	10	M	7.4
		6.0	17	F	3.8	15	F	6.5
		5.0	15	F	3.6	10	M	6.0
		6.7	8	M	2.3	10	M	5.6
		4.0	17	M	2.0	7	M	5.4
		6.8	10	F	1.0	8	M	4.9
		6.8	10	M	0.7	11	M	3.8
		2.8	12	M	0.7			
		6.7	14	F	0.4			
		6.7	8	M	0.3			
		4.5	16	M	0			
		4.5	16	M	0			
		4.8	16	F	0			
		3.5	16	F	0			
		4.0	17	M	0			
		11.4	13	M	0			
		11.4	13	M	0			
		5.4	6	M	0			
		6.5	9	F	0			
		10.0	12	F	0			
		13.5	14	F	0			
				Average	1.1			6.0

TABLE 1.—*Maximal Muscle Action Potentials for Children—(Continued)*

		A. Poliomyelitis				B. Normal[4]		
Nerve Stimulated	Muscles Recorded	Years Since Onset of Symptoms	Age, Years	Sex	Potential, Millivolts*	Age, Years	Sex	Potential, Millivolts*
	Dorsum of foot	4.7	7	M	9.4	16	F	9.0
		6.7	10	M	8.6	10	M	7.5
		4.6	17	F	5.0	14	F	7.4
		6.7	8	M	4.6	13	M	6.1
		4.0	17	M	4.3	12	F	6.0
		6.7	8	M	4.2	10	M	5.7
		5.0	15	F	2.8	9	F	4.5
		5.0	15	F	2.7	10	M	3.4
		2.8	12	M	2.5	8	M	3.0
		8.7	17	F	2.2			
		6.8	14	F	2.0			
		6.8	10	F	0.4			
		4.5	16	M	0			
		4.5	16	M	0			
		4.8	16	F	0			
		3.5	16	F	0			
		4.0	17	M	0			
		11.4	13	M	0			
		11.4	13	M	0			
		4.7	7	M	0			
		6.5	9	F	0			
		10.0	12	F	0			
		13.5	14	F	0			
		8.7	17	F	0			
				Average	2.0			5.8
Ulnar	Forearm	4.9	15	M	3.1			
		6.6	13	M	3.1			
		7.7	9	M	1.1			
				Average	2.4			
	Hypothenar group	6.6	13	M	4.7	14	F	10.0
		4.9	15	M	2.7	10	F	10.0
		7.7	9	M	0.2	10	M	8.1
				Average	2.5			9.4
Median	Forearm	6.6	13	M	5.8	10	F	8.2
		4.9	15	M	3.4	13	M	6.0
				Average	4.7			7.1
	Thenar group	6.6	13	M	4.9	14	F	9.5
						10	F	8.4
						13	M	7.4
				Average	4.9			8.4
Radial	Forearm	6.6	13	M	4.0	13	M	8.7
		4.9	15	M	4.0	10	F	7.8
				Average	4.0			8.2

*In tables 1 and 2, values for muscles of the forearm and leg were derived by averaging the maximal potentials found at several levels distal to the oleocranon or the tibial tuberosity. Potentials for the small muscles of the hand and foot were the maximal voltages obtained by placing the recording electrodes in many positions on the skin overlying these muscles. When repeated testing gave more than one figure for the same muscle group of an individual subject, these values were averaged.

and Kuffler[2]). The intensity of the shocks was usually twice that necessary to produce a maximal muscle action potential. Details of the stimulating and recording electrodes and positions for optimal stimulation of the several nerves are to be found elsewhere (Hodes, Larrabee and German[3]).

The muscle action potential was amplified by a three stage, condenser-coupled differential amplifier and photographed from a 5 inch (12.5 cm.) cathode ray oscilloscope on continuously moving bromide paper. The sensitivity of the amplifier was determined by calibration each time an experiment was performed.

RESULTS

Response to Single Maximal Shocks to the Motor Nerve.—The muscles from which electromyograms were obtained were all weak when tested clinically and presented various degrees of atrophy in different patients. In 41 of 125 trials no muscle potentials could be detected. In the remaining 84 trials values for maximal action potentials evoked by supramaximal motor nerve stimulation were from 0.2 to 13.0 millivolts. Only 15 potentials in this series exceeded 5 millivolts (table 1*A*). I obtained 58 records from the presumably unaffected extremities of 18 children, 7 to 16 years old, whose opposite limbs were partially or completely paralyzed by poliomyelitis. These potentials ranged from 3.0 to 18.9 millivolts, and values less than 5 millivolts were recorded in only 5 cases (table 1*B*).[4]

The average potentials for the muscles of the lower limb of patients with poliomyelitis (110 determinations) and for the muscles of apparently normal children (46 determinations) are given in table 2. The muscles of the leg were considerably more affected than were those of the foot—a finding that agrees with the clinical observation that the proximal muscles of the limbs are more likely to be paralyzed than are the distal muscles (Peabody, Draper and Dochez;[5] Lovett;[6] Nelson[7]).

Usually, the diphasic muscular response to a single maximal shock to the nerve remained of constant form, and its amplitude did not vary

2. Harvey, A. M., and Kuffler, S. W.: Motor Nerve Function with Lesions of the Peripheral Nerves: A Quantitative Study, Arch. Neurol. & Psychiat. **52**: 317-322 (Oct.) 1944.

3. Hodes, R.; Larrabee, M. G., and German, W. J.: The Human Electromyogram in Response to Nerve Stimulation, and the Conduction Velocity of Motor Axons: Studies on Normal and Injured Peripheral Nerves, Normally and After Peripheral Nerve Injury, Arch. Neurol. & Psychiat. **60**:340 (Oct.) 1948.

4. The "normal" values in tables 1 and 2 are given for comparison with the present series and are not to be considered normal for children in the age group of 7 to 16 years, since a small loss of power, due to involvement by poliomyelitis, may have been undetected on clinical examination.

5. Peabody, F. W.; Draper, G., and Dochez, A. R.: A Clinical Study of Acute Poliomyelitis, Monograph 4, Rockefeller Institute for Medical Research, 1912.

6. Lovett, R. W.: The Treatment of Infantile Paralysis: Preliminary Report, Based on a Study of the Vermont Epidemic of 1914, J. A. M. A. **64**:2118-2123 (June 26) 1915.

by more than 5 per cent during any particular experiment, lasting three to four hours. In a few instances, however, there was a gradual decline in the size of the action potential,[8] the greatest decrease being in a patient whose electromyogram at the termination of a long experiment showed only 84 per cent of the activity measured at the start of the examination. Such a finding resembles the fatigue produced by insufficient intervals of rest between successive muscular exertions described by Harvey and Masland[9] in patients with myasthenia gravis and by Wiersma[10] in patients with poliomyelitis. As will be discussed later, this fatigue is thought to be caused by a reduction in the number of activated muscle fibers resulting from the block of some motor nerve impulses at the neuromuscular junction.

TABLE 2.—*Average of Action Potentials for Muscles of the Lower Extremity of Children*

Nerve Stimulated	Muscles Recorded	Potential, Millivolts*		Percentage of Normal Potential
		Poliomyelitis	Normal[4]	
Tibial	Foot	5.0	11.5	43.5
	Leg	2.7	15.7	17.7
Peroneal	Foot	2.0	5.8	34.6
	Leg	1.1	6.0	18.3

*See footnote, table 1.

Response to Repetitive Nerve Stimulation.—When a normal muscle is stimulated maximally by way of its motor nerve at rates up to 40 per second for a few seconds, the action potentials remain constant throughout the period of excitation (Harvey and Masland[11]). The response of affected muscles in cases of poliomyelitis to brief repetitive motor nerve stimulation stands in striking contrast to the normal. Shocks delivered to the nerve 0.2 to 19 times per second produced a series of muscle responses in which both negative and positive deflections of the initial action potential were greater in amplitude and duration than the subsequent

7. Nelson, N.: Spinal Cord Circulation in Poliomyelitis, Science **104**:49-50, 1946.

8. Unless otherwise noted, descriptions of the "action potential," "electromyogram" and the like refer only to the negative phase of the response (upward deflection in the figures).

9. Harvey, A. M., and Masland, R. L.: The Electromyogram in Myasthenia Gravis, Bull. Johns Hopkins Hosp. **69**:547-565, 1941.

10. Wiersma, C. A. G.: Muscles Consisting of a Single Motor Unit After Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **61**:85-89, 1946.

11. Harvey, A. M., and Masland, R. L.: A Method for the Study of Neuro-Muscular Transmission in Human Subjects, Bull. Johns Hopkins Hosp. **68**:81-93, 1941.

potentials of the tetanus evoked by identical stimuli to the nerve. The rate and degree of decline varied from patient to patient and did not appear to bear any simple relation to frequency of the stimuli. The progressive subsidence to a minimum occurred by the fifth to the tenth stimu-

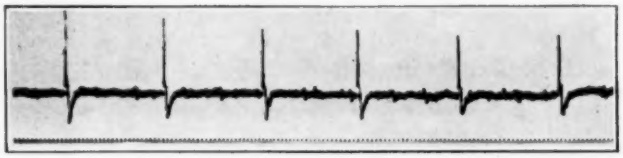

Fig. 1.—Progressive reduction in size of action potentials elicited by repetitive nerve stimulation. The response is that of muscles of the leg supplied by the tibial nerve to supramaximal stimulation at the rate of 2.6 times per second.

In this figure, and in figures 4, 5, 6, 9 and 10, the time interval between adjacent marks at the bottom is 16.67 milliseconds (1/60 second).

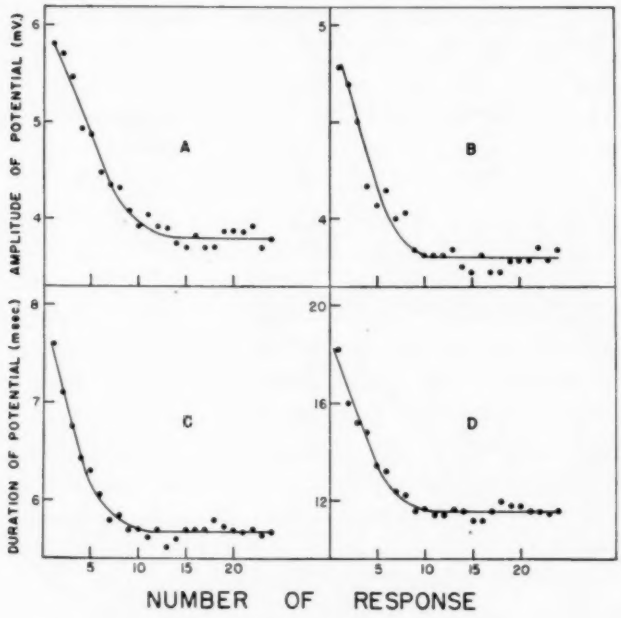

Fig. 2.—Graph showing changes in amplitude and duration of action potentials during tetanus. On the abscissa is plotted the number of the response in a train of impulses evoked by stimulation of the radial nerve at a rate of 19 times a second for 1.25 seconds; on the ordinate, the amplitude and duration of the negative (*A* and *C*) and positive (*B* and *D*) phases of the action potential.

lus, after which the response to continued excitation remained essentially constant.

Figure 1 illustrates the characteristic reduction in the potential during repetitive nerve stimulation 2.6 times per second. The amplitude of the last action potential is only 71 per cent of that of the first. Graphic

representation of the changes described is given for another experiment on a different patient in figure 2*A* and *B*.

The significance of changes in duration of the action potential will be considered later.

In patients with myasthenia gravis Harvey and Masland[9] noted changes in action potential similar to those described here. They concluded that the reduction of amplitude of potential during repetitive

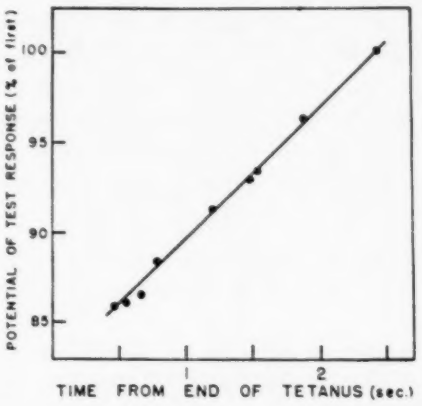

Fig. 3.—Recovery of size of response to test shock following stimulation of the radial nerve 12.4 times per second for 1.2 seconds. On the abscissa is plotted the time after end of the tetanic volley at which the test shock was applied to the nerve; the ordinate, the size of the action potential evoked by the test shock, expressed as the percentage of potential of the first response of the tetanus.

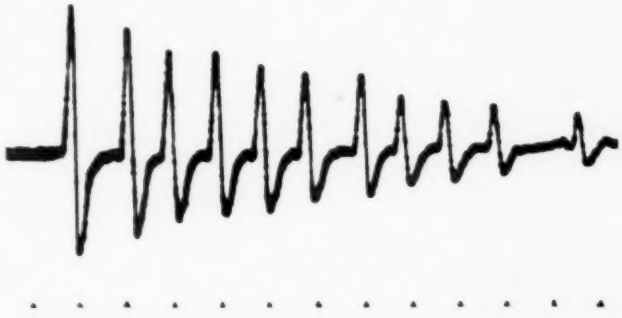

Fig. 4.—Electromyogram of the sole functional motor unit of the flexor digitorum brevis muscle of patient J. H. The subject was requested to plantar flex the fourth toe as vigorously as possible and to maintain the maximal tension possible. Duration of the first component of the action potential (3.4 milliseconds) is unchanged throughout.

stimulation gives evidence that fewer muscle fibers are activated by the second and by succeeding maximal shocks to the nerve than by the first. The same explanation is offered for the present findings in patients with poliomyelitis.

When single test shocks were applied to the nerve at variable intervals after the cessation of a tetanus of constant frequency and duration,

it was found that the greater the elapsed time, the more nearly the amplitude of the action potential produced by the test shock approached that of the first response to the tetanus. Figure 3 demonstrates that recovery from repetitive stimulation at a rate of 12.4 per second for 1.2 seconds was not complete until 2.4 seconds after the tetanus. After another series of conditioning shocks in the same patient at the same frequency, but lasting only 0.55 second, full recovery occurred within 1.8 seconds.

Response of the Motor Unit.—The electromyograms of voluntary muscular activity of 3 patients were simple enough to suggest that the surface electrodes were registering activity from a single motor unit. Electromyograms from these patients showed a striking decline in the amplitude of all action potentials subsequent to the first. Figure 4, taken during an attempt to maintain maximal plantar flexion of the fourth toe, is typical. By the sixth response the initial potential, of 0.30 millivolt, has fallen to 55 per cent of the first. The duration of the action potentials does not change throughout the contraction. This will be considered in detail later.

Some of the conclusions arrived at in this study are based on the assumption that figure 4 represents the activity of a single motoneuron and its associated muscle fibers. Therefore, further examination of patient J. H., whose flexor digitorum brevis muscle provided the electromyograms in figures 4 and 5, was undertaken.[12] The extensive data obtained have proved that these potentials are indeed contributed by the muscle fibers innervated by one nerve fiber. The complete evidence required to establish the unit neuronal character of the response will be given in a separate report. However, because of the considerable importance for this paper that is attached to accepting figure 4 as representing the activity of a single motor unit, it is deemed advisable to give a summary of the more important aspects of the proof:

1. There is a critical threshold for percutaneous electrical stimulation of the tibial nerve. When threshold intensity is reached, a maximal muscle potential is obtained (all or nothing response). This response is identical with the first potential of a voluntary contraction (compare initial spikes of figure 5*A* and *B*).

2. The response is identical in duration whether evoked voluntarily, reflexly or by motor nerve stimulation at the popliteal fossa or at the ankle (fig. 5). If the muscular response were produced by the participation of more than one motor axon, and if velocity of conduction in the nerve fibers differed by as little as 2.5 per cent, then there would be

12. This 16 year old boy was incapable of making any voluntary movement of the left extremity below the knee other than minimal plantar flexion of the fourth toe. Palpation revealed this motion to be achieved solely by contraction of the short flexor muscles of the toe.

an easily detectable difference in duration between the muscle action potentials with long and those with short distances of conduction along the nerve.

3. Results qualitatively similar to those shown in figure 4 may be obtained by repetitive supramaximal motor nerve stimulation. For example, the responses produced by stimulation of the tibial nerve at the popliteal fossa (indicated by arrows in figure 5*B*) clearly show the decline in magnitude of the muscle action potential to repeated electrical excitation of the nerve.

The conclusion thus appears inescapable that figure 4 represents the electrical activity of a single motor unit. It can be stated immediately, therefore, that not all the muscle fibers of a motor unit are excited by every impulse produced by repetitive nervous activity. This deficiency would thus be contributory to the characteristic reduction in amplitude of action potentials of the poliomyelitic muscle during a tetanus.

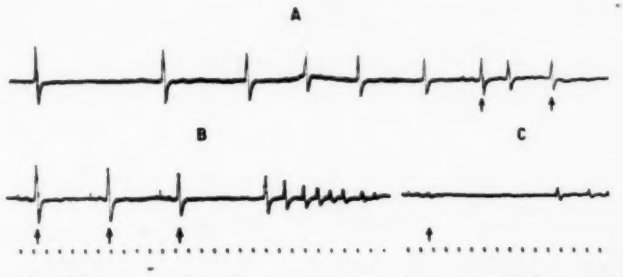

Fig. 5.—Combination of motor unit potentials caused by volitional effort and by stimulation of the tibial nerve at the popliteal fossa in the patient whose electromyogram is shown in figure 4. Potentials produced by stimulation of the nerve are marked by arrows. Between *B* and *C* the patient continued voluntary contractions. The first potential or record *C* occurred 0.82 second after the end of *B*.

Duration of the Action Potential.—In a poliomyelitic muscle supplied by more than one nerve fiber, diminution in the size of the electromyogram during brief repetitive nerve excitation is accompanied with a shortened duration of the action potential. Figure 6 shows the first and eighth responses of a series of nine action potentials elicited by maximal stimulation of a muscle in which several motor units have survived. These potentials last 7.8 and 6.2 milliseconds, respectively. Voltages of the corresponding responses are 2.1 and 1.6 millivolts. *C* and *D* in figure 2 show similar results from another experiment and illustrate the parallelism between decline in voltage and reduction in duration of potential.

In contrast with these observations on muscles supplied by more than one nerve fiber, careful measurement of many records involving only a single motor units reveals the fact that the duration of the unit action potential is unchanged in spite of a considerable reduction of voltage (figs. 4 and 5). If it is assumed that such temporal constancy of the unit muscle potential is a general feature of the activity of all motor

units, then the data presented in the preceding sections suggest that failure of some mucle fibers of several motor units is insufficient to account for all the abnormalities of the electromyogram which result from repetitive muscular activation in poliomyelitis. Such a failure could not explain the shortened duration of potential which has been shown to occur in a muscle innervated by more than one nerve fiber (figs. 2 and 6). The contribution of a second factor to the abnormal electrical response must therefore be considered, namely, the dropping out of action of entire motor units. Possible reasons for such defection of motor units will be given in the discussion of results.

Fig. 6.—Decrease of duration and magnitude of potentials in muscles supplied by more than one motoneuron. The potentials were produced by supramaximal stimulation of the radial nerve at a rate of 14 per second. The upper record is the first, and the lower is the eighth, potential in the series of nine. Duration of the first response was 7.8 milliseconds; that of the eighth potential, 6.2 milliseconds. Voltages of the corresponding electromyograms were 2.1 and 1.6 millivolts. *S* indicates stimulus artefacts. (The original of this record was retouched because the cathode ray tracing was too faint for satisfactory reproduction.)

Effect of Neostigmine.—A single subcutaneous or intramuscular injection of 1.0 to 1.5 mg. of neostigmine methylsulfate U.S.P. and 0.007 to 0.01 grain (0.4 to 0.6 mg.) of atropine sulfate was given to 6 patients who exhibited the characteristic peripheral neuromuscular defects of poliomyelitis.

In 4 cases there was, after administration of the drug, a small increase (2 to 12 per cent) in the size of the action potential evoked by single shocks. Figure 7*A* shows such an effect in a case in which the peroneal nerve was stimulated twice per second. Since there was no evidence of repetitive muscle response to a single stimulus, such a result indicates that there exist some muscle fibers which, though innervated, are not excited by a single maximal shock in the absence of neostigmine. A

similar result was reported in patients with myasthenia gravis by Harvey, Lilienthal and Talbot.[13]

Another effect of the drug was observed in the reaction of the muscle to tetanic nerve stimulation. It can be seen from figure 7, curves *B* and *C*, which show the responses to the second and fifth stimuli, respectively, that the electromyogram was maintained better during repetitive stimulation following injections of neostigmine than prior to the medication. In figure 8 is charted a complete experiment on another patient. It similarly

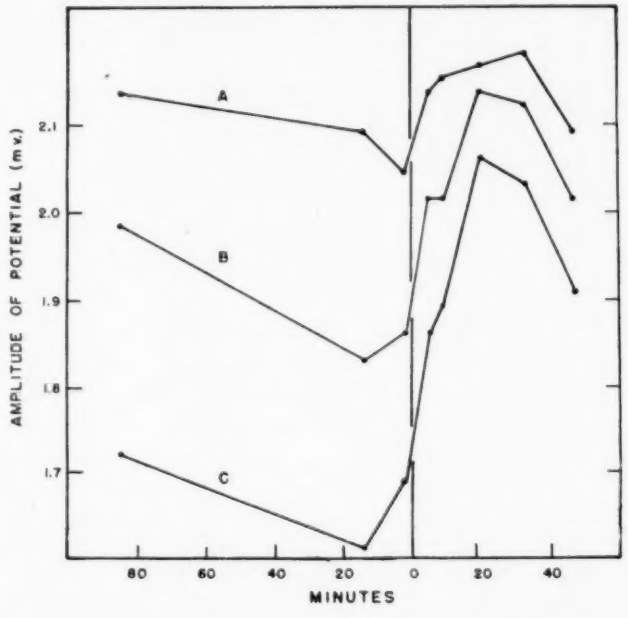

Fig. 7.—Effect of neostigmine methylsulfate on potentials produced by muscles of the leg in response to stimulation of the peroneal nerve twice a second. On the ordinate is plotted the amplitude of potential; on the abscissa, the time before or after intramuscular injection of 1.0 mg. of neostigmine methylsulfate. Curve *A* represents the size of the first potential of each tetanus; curves *B* and *C* show the amplitude of the second and fifth responses, respectively.

demonstrates the effect of this substance in preserving the size of the muscle action potential at a higher value during repetitive activation (thirty-eight minutes after injection) than that which occurs in the absence of drug therapy.

Only 2 experiments were available in which the duration of the potential could be measured accurately before and after administration of neostigmine methylsulfate. There was no demonstrable effect due to

13. Harvey, A. M.; Lilienthal, J. L., Jr., and Talbot, S. A.: Observations on the Nature of Myasthenia Gravis: The Phenomena of Facilitation and Depression of Neuromuscular Transmission, Bull. Johns Hopkins Hosp. **69**:547-565, 1941.

action of the drug on the duration of the response evoked by single or repeated supramaximal nerve volleys.

It should be mentioned that our information on the duration of the effect of a single dose of neostigmine methylsulfate on poliomyelitic muscle is too scanty to be of much value. The apparent reduction of efficacy twenty to thirty-three minutes after injection in the patient whose

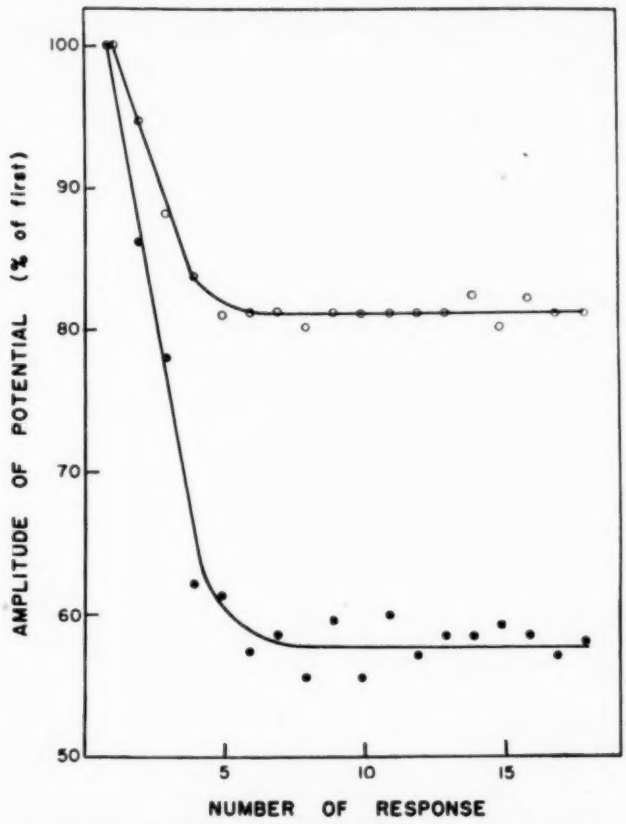

Fig. 8.—Effect of neostigmine methylsulfate on potentials from muscles of the forearm innervated by the radial nerve in a different patient than the one represented by figure 7. The nerve was stimulated at the rate of 8 times per second. On the abscissa is plotted the number of the response in the series; on the ordinate, the amplitude of the action potential, the voltage in the first response being used as 100 per cent. Filled circles indicate values before injection of neostigmine methylsulfate: open circles, values thirty-eight minutes after intramuscular injection of 1.0 mg. of neostigmine methylsulfate and 0.007 grain (0.4 mg.) of atropine sulfate.

responses are shown in figure 7 was not observed in 2 other patients in whom no sign of reduction of effect was detected thirty and eighty minutes, respectively, after parenteral administration of the same amount of neostigmine methylsulfate.

No attempt was made to increase the dose of the drug to determine whether a normal electromyogram could be produced in response to

tetanic excitation. It was felt that such trials would be most successfully performed in conjunction with a separate series of clinical experiments designed to study this point specifically.

COMMENT

The abnormal response of the poliomyelitic muscle to repetitive activation must be due to deranged function of one or more of the follow-

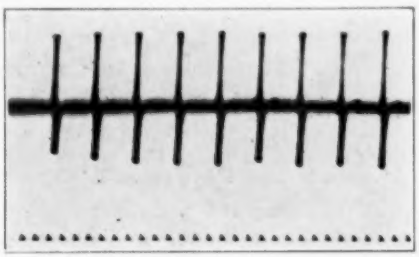

Fig. 9.—Progressive increase of muscle potentials during stimulation of the tibial nerve, at a rate of 20 times per second, in a patient with poliomyelitis. Recording electrodes were on the sole of the foot.

ing structures: the peripheral nerve fiber, the neuromyal junction or the muscle fiber. Temporal dispersion of the muscle fiber response cannot explain the progressive diminution of amplitude observed, since this would produce an increase in the duration of the electromyogram. Nor

Fig. 10.—Potentials from muscles of the leg, distribution of the peroneal nerve, in a normal subject. The nerve was stimulated at the rate of 30 times per second. Note the striking diminution in duration and increased amplitude of action potential. Stimulation of the nerve continued for several seconds after the end of the record, but there was no further change in amplitude or duration of the potential.

is it likely that a reduction of potential of each muscle fiber is the cause of the abnormality, for neostigmine is not known to have a direct action on the conducted muscle response. Also, failure of the nerve fiber to respond would not account for all the electromyographic findings, since the potential of the single motor units falls off progressively, rather than in an all or nothing fashion (fig. 4). Because of these considerations, and also because the action of neostigmine methylsulfate which we have

observed resembles its well known action at the neuromyal junction, it would appear reasonable to fix the locus of at least part of the faulty response in cases of poliomyelitis at the junctional region, as in cases of partial curarization and myasthenia gravis (Harvey and Masland[9]).

It has been suggested previously (p. 466) that entire motor units might fail in the course of repeated activity. Such unresponsive motor units might result from a defect in the nerve fiber, from a synaptic block at every neuromyal junction supplied by one motoneuron or from an insufficiency of every muscle fiber innervated by one motor axon. Further work is required to determine whether the peripheral lesion of poliomyelitis includes nerve and muscle, in addition to the junctional defects described here.

Our data confirm the findings of Bentsen,[14] who noted in patients with chronic poliomyelitis a fall in the size of the muscle action potentials (needle electrodes) during sustained voluntary effort. In addition, we have shown that at least part of the responsibility for such abnormality is localized at the neuromyal junction. The material in this paper thus provides evidence for the existence, in human poliomyelitis, of a defect neither resident within the central nervous system nor necessarily the direct result of a central impairment. Bentsen's report that "fatigue" (decline in size of potential) was not present earlier than forty-eight days after the onset of symptoms offers an important lead for further study.[15] It would be instructive to determine additional differences between the neuromuscular apparatus before and after the establishment of the conditions resulting in abnormal junctional transmission.

In patients with chronic poliomyelitis Wiersma[10] observed an increase in the size of muscle potentials from a motor unit during voluntary contraction. He proposed, therefore, that the repetition of nerve impulses causes facilitation at the neuromyal junction and brings into action some muscle fibers of the motor unit which are not excited at the start of the willed movement. On the contrary, our observations have not suggested junctional facilitation in poliomyelitic patients. Possible explanations should be attempted for the apparent discrepancies between the results given by Wiersma and those cited in the present paper and also by Bentsen. For example, the state of the neuromuscular apparatus of Wiersma's patients may have differed from that of our patients, since most of his

14. Bentsen, K. G., cited by Buchthal, F., and Høncke, P.: Electromyographical Examination of Patients Suffering from Anterior Acute Poliomyelitis up to Six Months After the Acute Stage of the Disease, Acta med. Scandinav. **116**:148-164, 1944.

15. In some of our earlier experiments (unpublished) on poliomyelitis, a note in one protocol states that the patient, tested one hundred and thirty-five days after the onset of symptoms, exhibited muscle potentials which declined in amplitude subsequent to the first response. Maximal stimulation of the motor nerve once every two seconds lasted twenty seconds.

patients had undergone treatment by the neurotripsy method of Billig,[15a] which has been shown by Hodes[15b] to produce changes at the neuromyal junction. Another such reason would be available, is as a result poliomyelitis both excitatory and depressant influences affected the activity of the neuromyal junction, either concomitantly or at different stages of the disease, and some unknown conditions in Wiersma's experiments may have been favorable for revealing facilitation, whereas the conditions of our study uncovered only the depressant action of the disease. It is pertinent to note here that Harvey, Lilienthal and Talbot[13] found simultaneous facilitation and depression at the neuromyal junction in a patient with myasthenia gravis.

It should be mentioned that in the present study it was noted that tetanic motor nerve stimulation both in patients with poliomyelitis and in a normal subject occasionally produced action potentials which gradually increased in size and decreased in duration (figs. 9 and 10). In Wiersma's figures 1 and 4 it is also apparent that the spikes of increased voltage which occur late in the contraction last a shorter time than the initial potential. A reduction in duration of potential is difficult to reconcile with an increase in the number of active muscle fibers, for Brown and Harvey[16] and Harvey, Lilienthal and Talbot[13] have shown that junctional facilitation is accompanied with an increased duration of the response. Either of the following two explanations would account for the observed changes in potential described by Wiersma, and illustrated in figures 9 and 10: 1. With diffuse recording by means of surface electrodes, the activity of some muscle fibers may register as a large positive and a small negative potential. If such fibers were to become inactive (due to junctional block) at a time when the negative voltage of most of the other muscle fibers was rising to its peak, a net gain in negativity could result as a consequence of this loss of voltage of opposite sign. A similar argument, with the polarities reversed, could explain an increased positive potential. 2. The electrical responses may become more nearly synchronous as a result of continued stimulation and cause potentials of increased size and shortened duration. Findings capable of such an interpretation were reported in the electromyograms of normal human muscle by Harvey and Masland.[11]

An increase in size of potential resulting from repetitive nerve action, therefore, need not be taken to express an abnormality characteristic of poliomyelitis, since an apparently similar phenomenon has been observed

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15a. Billig, H. E.; van Harrevald, A., and Wiersma, C. A. G.: On Reinnervation of Paretic Muscles by Use of Their Residual Nerve Supply, J. Neuropath. & Exper. Neurol. **5**:1-23, 1946.

15b. Hodes, R.: Muscle Action Potentials in Human Poliomyelitis Before and After Closed Manual Neurotripsy, Am. J. M. Sc., to be published.

16. Brown, G. L., and Harvey, A. M.: Neuro-Muscular Conduction in the Fowl, J. Physiol. **93**:285-300, 1938.

in the normal muscle. Nor do such results require for their explanation facilitation at the neuromuscular junction. On the contrary, because of our findings for the whole muscle and the motor unit, and the results of neostigmine therapy, it is our belief that the disease alters the junctional region in such a way that the transmission of a nerve impulse is followed by synaptic depression.

Since 1943, when Kabat and Knapp[17] first employed neostigmine therapy in poliomyelitis, several clinical trials of the drug have suggested its usefulness in treatment of this disease.[18] With the exception of Geyerhahn's[19] work, these investigations were carried out on patients in the acute or the subacute stage of the disease and dealt mainly with the effect of neostigmine on muscle spasm and incoordination. The criteria for improvement of muscular function employed by these workers thus do not apply to the data in this paper.

Our observations on the motor unit make it clear that the peripheral defect in poliomyelitis becomes apparent not only during artifical stimulation of the motor nerve but during naturally induced somatic motor activity. The muscular fatigue experienced by Geyerhahn's[19] patient with chronic poliomyelitis may thus be explained as the result of the neuromuscular consequences of this disease which I have described. Because of Geyerhahn's success and the encouraging preliminary results in the present experiments, the use of neostigmine as a therapeutic agent for the restoration of muscle power and as a deterrent to fatigue in cases of chronic poliomyelitis should be studied on a larger group of patients. Such an investigation should attempt to establish an adequate dose and should include estimations of muscular strength and fatigue for correlation with electromyographic findings. Furthermore, by heeding the clue given by Bentsen,[14] one may discover distinctions between the pathologic changes and symptoms of the acute infection and its sequelae in the course of such experiments.

Our data dispose of the concept of anterior poliomyelitis as a disease involving the central nervous system exclusively. These findings leave unanswered the important question, raised by Chor,[20] Hassin,[21] Carey

17. Kabat, H., and Knapp, M. E.: The Use of Prostigmine in the Treatment of Poliomyelitis, J. A. M. A. **122**:989-995 (Aug. 7) 1943.

18. Bibliography: The Clinical Use of Prostigmine, Roche Rev. **10**:305-331, 1946.

19. Geyerhahn, G.: The Use of Prostigmine in Arrested Poliomyelitis, J. Maine M. A. **36**:95, 1945.

20. Chor, H.: Nerve Degeneration in Poliomyelitis: Changes in the Motor Nerve Endings, Arch. Neurol. & Psychiat. **29**:344-358 (Feb.) 1933.

21. Hassin, G. B.: Landry's Paralysis: Its Clinical and Pathological Features, J. Neuropath. & Exper. Neurol. **2**:293-300, 1943.

and co-workers[22] and others, of how the peripheral defect originates—whether by extension of morbid processes from the central nervous system or other parts of the body to the junctional region or by direct action of the virus on the neuromyal junction.

SUMMARY AND CONCLUSIONS

1. On a series of 22 patients with chronic poliomyelitis the following observations were made:

(*a*) The muscle action potentials elicited by single maximal stimuli to the motor nerve of the affected muscles were smaller than those from corresponding normal muscles. The intrinsic muscles of the foot were less affected than were the muscles of the leg.

(*b*) The electromyogram resulting from brief maximal repetitive motor nerve stimulation (0.2 to 19 per second) in patients with chronic poliomyelitis was abnormal. The successive responses were smaller in amplitude and of shorter duration than the first response.

(*c*) The time course of the electrical response of the motor unit during brief voluntary effort or repetitive nerve stimulation was unchanged, although the spike amplitude declined progressively.

2. The following conclusions are drawn:

(*a*) The peripheral defect is due to the failure of some muscle fibers of many motor units to be excited, and probably also to the dropping out of action of entire motor units.

(*b*) Defective function at the neuromyal junction adequately explains the peripheral pathologic changes.

3. Neostigmine methylsulfate partially restored the abnormal electrical response; its therapeutic use is therefore suggested.

4. The clinical significance of these observations is discussed.

Dr. George Morris Piersol, Dr. Walter S. Cornell, Dr. de Forrest Willard, Dr. Joseph Stokes Jr. and Dr. Burton Chance Jr. and other members of the Medical Advisory Board of the Philadelphia chapter, National Foundation for Infantile Paralysis, Inc., assisted in selecting the patients; Mrs. E. Lois Bateman, of the Emergency Aid of Pennsylvania, helped in transporting the patients; Dr. Samuel Peacock Jr. assisted in the technical details of the experiments; Mr. Joseph Bruno and Miss Elizabeth O'Dwyer made the checks on muscle function; Dr. Donald Jones gave clinical advice, and Mr. Warren Founds Jr., of the Johnson Foundation, made the photographic reproductions of the original records.

University of Pennsylvania Hospital.

22. Carey, E. J.: Effects of Poliomyelitis on the Neuromuscular Mechanisms in the Monkey, Am. J. Path. **20**:961-965, 1944. Carey, E. J.; Massopust, L. C.; Zeit, W., and Haushalter, E.: Anatomic Changes of Motor Nerve Endings in Human Muscles in Early Poliomyelitis, J. Neuropath. & Exper. Neurol. **3**:121-130, 1944.

REFLEX DYSKINESIA IN CHILDREN

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THE OVERACTIVE child remains a topic of prime interest to the diagnostician and the therapeutist. The various sources of overactive behavior in childhood have recently been surveyed by Schneider.[1] Their proper differentiation is a goal that will still require much concerted effort on the part of all workers dealing with this problem.

The basic understanding of overactivity in children, although remarkably advanced by progress in psychologic testing and analysis, is often handicapped by incompleteness of examination, by lack of awareness of the various organic factors involved and by failure to appreciate their importance. The neurologic testing of children presenting overactive behavior is no doubt an indispensable requisite for the objective evaluation of the etiologic possibilities. Moreover, it remains doubtful whether the time-honored technic of simple observation will permit a final judgment as to the nature of abnormal behavior patterns unless aided by special investigations which the individual case may require. The need for a study of the postural reactions has been emphasized by Teicher.[2] Assistance rendered by electroencephalographic, cinematographic and other laboratory procedures is frequently unavailable. Familiarity with the aspects of neuromuscular maturation and with methods of calculating various grades of motor development, however indispensable, will become, it is hoped, a more readily available tool of the examiner's clinical equipment.[3]

At the present stage of events, the experienced clinician will not light-heartedly forego the benefits to be derived from the elementary neurologic approach and from testing of the ordinary reflexes, which is

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From the Neurological Department of the Mental Hygiene Clinic, Delaware State Hospital.

1. Schneider, W. F.: J. Pediat. **26**:559-570, 1945.
2. Teicher, J. D.: J. Nerv. & Ment. Dis. **94**:277-304, 1941.
3. McGraw, M. D.: The Neuromuscular Maturation of the Human Infant, New York, Columbia University Press, 1943. Gesell, A., and Amatruda, C. S.: Developmental Diagnosis, ed. 3, New York, Paul B. Hoeber, Inc., 1941. Oseretsky: The Oseretsky Tests of Motor Proficiency, translated and edited by E. A. Doll, Minneapolis, Educational Test Bureau, 1946.

liable to yield information not obtainable in any other way. This holds true for phenomena which, while not strictly reflexes in accordance with the definition of Wartenberg,[4] have, nevertheless, the attributes of reflex reactions and are elicited in a reflex manner. Such phenomena seem to be commoner than has hitherto been realized. It is the purpose of this paper to demonstrate them in the instance of dyskinetic syndromes.

Whereas the classic dyskinesias of extrapyramidal genesis are numerous, the reactive, or reflex, dyskinesias are comparatively rare. They have been the object of casual observation, but few students have favored them with any serious attention, although they merit further study.

The extrapyramidal forms of involuntary overactivity are usually described as hyperkinetic states and are so named, in contrast with hypokinetic and akinetic states. Because nowadays there exists a tendency to call hyperkinetic any odd type of hypermotility or overactive behavior in children, the term dyskinesia should remain reserved for certain clinical pictures of extrapyramidal origin which fall under the amyostatic symptom complex, the conception of which is attributed to Strümpell (Bing[5]), and which has since been amplified and further elaborated by the studies of Kleist, Herz and others.[6]

Accurate clinical observation has led to the differentiation of several dyskinetic syndromes, of which tremor at rest, chorea and athetosis are the best known examples. The dystonic syndrome has received thorough attention from Herz.[7] Elaborate technics, such as motion picture analysis, have led to a better understanding of the phenomenologic aspect but are, as a rule, unessential for purposes of gross classification. Rather, by depending on observation alone is it possible, in the majority of cases, to determine the type of involuntary movement with a fair degree of accuracy.

Some confusion of terminology still mars the picture. For instance, "congenital chorea" is used in the literature as descriptive of Huntington's chorea and of neonatal or postnatal chorea. Some students have insisted that certain forms of dyskinesia are indistinct in type, apparently owing to mixed features, resulting in classification as choreoathetosis and in such designations as athetoid and choreiform.

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4. Wartenberg, R.: The Examination of Reflexes, Chicago, The Year Book Publishers, Inc., 1945.

5. Bing, R., and Haymaker, W.: Textbook of Nervous Diseases, St. Louis, C. V. Mosby Company, 1939.

6. (*a*) Herz, E.: J. f. Psychol. u. Neurol. **43**:1-182, 1931. (*b*) Herz, E., and Putnam, T. J.: Motor Disorders in Nervous Diseases, New York, King's Crown Press, 1946.

7. Herz, E.: Dystonia, Arch. Neurol. & Psychiat. **51**:305-355 (April) 1944; **52**:20-26 (July) 1944.

As to the character of their outward appearance, it is assumed that the reflex forms of hyperkinesia or amyostasis do not materially differ from those described as involuntary, spontaneous or automatic except by their dependence on some sort of stimulus for their origination and precipitation.

It is a matter of common experience—and this will be more clearly outlined later—to observe modification of involuntary and spontaneous hyperkinetic reactions by certain stimuli in a varying manner. This fact should not preclude the acceptance of dyskinetic movements as strictly reactive, or reflex, in character, provided that two conditions are fulfilled. First, involuntary and automatic movements should be absent, or they should, if present, be abortive and rudimentary. Secondly, the development of pronounced dyskinetic activity should remain in strict relation to stimulation, so as to assume virtual independence of the concomitant spontaneous and reactive phenomena.

Reflex dyskinesias may be grossly subdivided into three categories: reflex athetosis, reflex tremor and reflex chorea, in the order of their expected frequency. Cases of reflex athetosis have been reported by Alexander,[8] Herz[6a] and Jacoby.[9] No case of reflex tremor seems to exist in the available literature. However, 1 such case which I studied will be made the object of a separate communication.[10] Nothing certain is known in regard to the existence of reflex chorea, although some phenomena, to be described, may qualify for this category.

REPORT OF CASES

The following case studies will serve to exemplify the conditions in which reflex dyskinetic phenomena may be elicited, and to establish their characteristics in regard to the procedure of activation and to their manner of appearance.

OBSERVATION 1.—J. T. R., a white boy aged 8 years, presented a history of mastoiditis at the age of 4, followed by overactive behavior. He was referred to the Mental Hygiene Clinic as a conduct problem. His findings were insincerity, thieving and truancy. He was slow in walking and dragged his right foot. There was a history of masturbation and nocturnal enuresis.

Delivery had been normal. He was circumcised at birth. He started to talk at 13 months of age. He pulled himself up to a standing position at the age of 9 months, but did not walk until he was 2 years old. At the age of 3 months he had pneumonia, diarrhea and convulsions. At the age of 2 years he had laryngeal diphtheria, was hospitalized and had another convulsion. An attack of acute gastroenteritis and bilateral otitis media occurred in 1939. There was a period of treatment in the hospital for acute tracheobronchitis in 1941. A recurrence of

8. Alexander, L.: J. f. Psychol. u. Neurol. **44**:177-252, 1932.
9. Jacoby, G.: J. f. Psychol. u. Neurol. **46**:1-21, 1933.
10. Gordon, G. J.: Personal observation, to be published.

otitis media took place in 1944. Psychometric studies in May 1946 placed him in the group of low average intelligence.

Neurologic examination, on June 5, 1946, revealed the following abnormalities: slight involuntary unrest of the facial muscles, of choreiform appearance; variable deviation of the tongue of slight extent to one side or the other, and variable dyskinetic movements of the fingers of the opposite hand, precipitated by forceful closure (squeezing) of the hand. Stroking the skin over the medial aspect of the tibia (Oppenheim[5]) caused no reaction on the left side and was not followed by any movement of the toes of the opposite side. The same maneuver, executed on the right side, precipitated flexion of the toes on the right side and several complete cycles (four or five) of alternating flexions and extensions of the toes on the opposite (left) side. These reactions could be duplicated without any difficulty by renewed application of the Oppenheim maneuver.

This observation thus combines evidence of an abortive automatic dyskinesia, dyskinetic movements taking the place of synkinetic reactions, and a reflex dyskinesia of the rhythmic alternating type (rhythmokinesia).

Observation 2.—T. G., a white boy aged 6 years, had a somewhat obscure history. He was one of seven children, whose mother died. The boy had been raised with his younger brother (observation 3, F. G.) in an orphanage. He was described as physically neglected, with pediculosis, impetigo, symptoms of rickets, undescended testes, enuresis and attentional defect. Psychometric studies showed him to be retarded in the verbal sphere, manual minded and of low average intelligence. He was left handed and endowed with poor muscular coordination.

Neurologic examination on Oct. 2, 1946 revealed the following abnormalities: The deep muscular reflexes were generally active; plantar reflexes were present and of flexor type and were equal on the two sides; they were accompanied with slight equidirectional movements of the toes on the opposite side (synkinesia). The Oppenheim maneuver on the left side resulted in dorsiflexion of the left big toe but no evidence of contralateral reaction. The same procedure on the right side precipitated a whole cycle of extensions and subsequent flexions of the homolateral toes and dorsiflexion only of the contralateral (left) toes (synkinesia). Active bending of the knee against passive resistance, individually tested, resulted in extension of the toes on both the same and the opposite side and in slight flexion of the opposite knee (synkinesia).

Examination on Dec. 4, 1946 revealed involuntary movements, mainly in the legs; either synchronous plantar flexions of the feet and toes on the two sides or, more rarely, asynchronous, i.e., isolated dorsiflexion of the toes on the left side.

Plantar flexor reflexes with a normal homolateral flexor response but variable contralateral (synkinetic) reactions were obtained as follows: On stimulation of the left sole there was observed spreading of the toes or abortive dorsiflexion or rather discrete mixed movements of the toes of the right foot. On stimulation of the right sole there was a variable response of the toes of the left foot, either plantar flexion of all the toes or dorsiflexion of the left big toe.

Examination on March 5, 1947 revealed mild spontaneous motor unrest of the toes in total absence of stimulation and fairly good motor control of the separated fingers, while the wrists were invariably held in semiflexed position.

Plantar reflexes were of flexor type, with contralateral reactions (synkinesia), varying in extent and direction. These responses were always more intense in the left foot on stimulation of the right sole, with dorsiflexion of the left big toe and

plantar flexion of the four lateral toes (mixed movement response) the most frequent.

In review, this observation is marked by mild automatic dyskinesia, synkinetic reactions of great variability, a homolateral reflex dyskinesia of composite appearance and hyperreflexia.

Observation 3.—F. G., the 4 year old brother of the preceding patient, shared with him the handicaps of an unfavorable home atmosphere and extreme physical neglect. His conduct disturbance included stubbornness, destructiveness, sloppy eating manners and enuresis. Physically, there was failure of descent of the testes. Psychometric examination revealed a strong laterality conflict, retardation of speech development and a borderline rating of manual performance, keeping him out of the defective group.

Neurologic examination on Oct. 2, 1946 yielded the following deviations: somewhat poor ocular convergence movements; tremor of the closed eyelids; tremor and slight, irregular deviations of the tongue on protrusion; tendency to involuntary fanning of the fingers of the right hand during passive manipulation;

Essential Abnormalities in Behavior in Three Children with Reflex Dyskinesia

Observation	1	2	3
Abortive automatic dyskinesia	+	+	+
Synkinesia (contralateral dyskinesia)	+	+	+
Type of dyskinetic reactive movement	Rhythmic, alternating (contralateral), rhythmokinetic	Composite (homolateral)	Variable (homolateral) and composite (contralateral)
Increased tonus (hyperreflexia)	+	+	+

voluntary spreading of the fingers, accomplished with flexion of the wrist, and irregular, involuntary motor unrest, however mild, of the individual fingers. The deep muscular reflexes were uniformly active. The quadriceps reflexes were occasionally followed by a few clonic movements; however, no genuine patellar clonus was obtainable. The plantar reflexes were variable, both in extent and in direction of the movements of the toes. The Oppenheim maneuver resulted in bilateral extension of the toes when executed on either side. A similar reaction with flexion of the opposite knee was initiated by active bending of either knee against passive resistance. The toes were "restless" when the patient stood in the Romberg position.

On March 5, 1947, the Oppenheim maneuver on the left side engendered variable dorsiflexion of the toes of the left foot with abduction of the fifth toe and synkinetic dorsiflexion of the big toe of the right foot. Occasionally, the right big toe went through a whole cycle, or a one and a half cycle, movement (extension, flexion, extension). Similar reactions with contralateral movements of complex appearance were obtained from the right side (synkinesia).

In summary, the following abnormal features were obtained: variability of reflex pattern (e.g., plantar reflexes), spontaneous dyskinesia

of athetotic type, synkinesias and hyperreflexia, as well as tremor of the lid and difficulty in ocular convergence.

While it may appear unusually forceful to attempt classification of these observations under a single heading, it will not be inappropriate to select the outstanding features of the cases for purposes of comparison. This is easily achieved by tabulation of the essential abnormalities (table).

In other words, the previously cited observations reveal coincidence of four basic components: automatic dyskinesia, synkinetic dyskinesia, reflex dyskinesia and hypertonus. The character of the automatic or spontaneous dyskinesia in these instances needs no further discussion.

COMMENT

Synkinesias are referred to as those reactions of the opposite limbs, partly homologous and equidirectional in type, partly deviating from the homolateral reaction and variable in appearance. Whenever variable, they may seem almost indistinguishable from spontaneous dyskinetic movements.

The reflex dyskinesias, whether homolateral or contralateral, may be arbitrarily graded as follows: (1) variable and single movement responses; (2) composite movements (e.g., single cycle or one and a half cycle reactions), and (3) multiple cycle, alternating or rhythmic reactions.

The variable and single movement responses are those in which successive stimulation leads to entirely different reactions at different moments of testing. It is common, for instance, to find a complete reversal of the first noted reaction within a few seconds, so that initially a mild flexion, then no reaction at all and shortly afterward an extension movement result. This variability in reflexes is apparently an essential part of the intrinsic innervational changes characteristic of spontaneous dyskinesias. The term "polykinetic reflexes," used by Achard,[11] may apply to the same or to a similar form of reaction. Denny-Brown[12] recently indicated that the reflex response in spontaneous athetosis is variable and dependent on the phase of movement. Similar phasic changes were apparent under the influence of reflex stimulation in the present cases. There is no reason to believe that such changes occur at regular intervals. On the contrary, they develop irregularly and discontinuously, so as never to permit the examiner an accurate forecast of the reaction next observable. In the present cases, this pattern of reflex variability is readily demonstrable in the responses of the toes subsequent to stimulation of the

11. Achard, C.: Rev. gén. de clin. et de thérap. **47**:785-792, 1933.

12. Denny-Brown, D.: Diseases of the Basal Ganglia and Subthalamic Nuclei, New York, Oxford University Press, 1946.

sole or to the Oppenheim maneuver. Occasionally, it occurs that a fairly definite and uniform reaction is observed on several successive stimulations before the form of response veers to the opposite direction. Dorsiflexions of the toes, obtained in such circumstances, are not identical with the spastic extensor response of the classic Babinski phenomenon or any of its numerous modifications. The former movements are not pyramidal, but extrapyramidal and athetotic.

The composite movements of reflex dyskinesia are made up of a movement complex involving either a whole cycle, such as initial flexion followed by extension and vice versa, or a one and a half cycle movement, such as initial dorsiflexion followed by plantar flexion and return to the extensor position. In other words, either one or two shifts in the direction of movement are seen in fairly rapid, although not necessarily in regular, succession during the period of stimulation. It cannot be stated, however, that the constituent elements of such a complex have to be equally long. Neither does it appear that such complex movements can be invariably obtained. Their appearance seems to be rather infrequent and casual. This type of reflex movement should not be confounded with movement forms of mixed appearance, observed in similar circumstances, namely, dorsiflexion of the big toe with plantar flexion of the other toes, and innumerable other variants.

Quite different from the former reactions are those described as alternating, pluricyclic or rhythmic. Such reactions, consisting of alternating movements of the limbs, are usually spontaneous, but may occasionally depend on some sort of stimulus for their activation. They are described in the literature as rhythmic hyperkinesias of the limbs. It is doubtful whether these movements have any relation to the so-called rhythmias of Wilson.[13] Cases of rhythmic hyperkinesia of extremities have been reported by Patrikios,[14] Mezei[15] and Mussio-Fournier and associates.[16] The pattern of these movements actually varies from one observation to the other and gives the impression of considerable divergence in regard to the anatomic distribution of the lesion and to the nature of the pathologic substratum.

The form of rhythmokinesia, included in the first observation, is, by contrast, entirely reflex, having no counterpart in the spontaneous dyskinetic phenomena seen in the same patient. At the same time, it reveals a regular sequence of its constituent elements throughout its duration. It is limited to a rather small number of identical cycles and apparently

13. Wilson, S. A. K., and Bruce, A. N.: Neurology, Baltimore, Williams & Wilkins Company, 1940, vol. 2.

14. Patrikios, M. J.: Rev. neurol. **69**:64-65, 1938.

15. Mezei, B.: Ztschr. f. d. ges. Neurol. u. Psychiat. **171**:680-684, 1941.

16. Mussio-Fournier, J., and others: Rev. neurol. **72**:693-704, 1939.

cannot be indefinitely sustained by continued stimulation. Besides, it is contralateral and may have synkinetic character.

Reflex rhythmokinetic movements could be readily mistaken for clonic movements; yet the procedure of elicitation of the two is quite different, and this difference cannot be sufficiently emphasized.

The position of the rhythmokinesias within the group of dyskinesias is not altogether clear. This is the reason that it is difficult to take a more definite stand, especially after Herz,[6a] obviously with good reason, has discounted the choreatic provenience of spontaneous alternating limb movements in one of his observations. On the other hand, Russetzky[17] expressed the belief that automatic movements of this type, while representing an independent dyskinetic group, are part and parcel of Hunt's choreoathetosis or of O. Foerster's rhythmic combined tic.

Reflex dyskinesias may be either homolateral or contralateral to the site of stimulation. When contralateral, they may theoretically have the significance of synkinesias. While the homolateral motor phenomena appear mainly activated by stimuli applied to the skin or underlying structures (periosteum), such as touch, pain or pressure, contralateral or synkinetic responses may depend to a large extent on motor or kinesthetic stimuli. The studies of Alexander[8] and Jacoby[9] seem to support this hypothesis.

Considered as a group, all phenomena of reflex dyskinesia in my observations are bound to a state of hypertonus and, therefore, are classifiable as athetotic, with the exceptions previously discussed. Their athetotic nature is still further illuminated by their linkage with synkinesias the form of which was clearly dyskinetic in the present cases.

It is pertinent to stress the ubiquitous occurrence of synkinesias in the motor disturbances of infancy. Synkinetic movements were considered evidence of motor debility by Dupré and Merklen,[18] in conjunction with enuresis (Heuyer and Roudinesco[19]). In his study on motor infantilism, Jacob[20] mentioned the occurrence of athetoid movements as synkinesias of purposive and normally executed movements. Krauss[21] described synkinesias as residual symptoms of chorea minor. Hempel[22] noted interference of purposive acts by synkinesias in his observations on abortive athetosis.

To all appearances, the coincidence of synkinesias with spontaneous and reflex dyskinetic activity is not fortuitous. It is meaningful and serves to enrich knowledge of the various motor disorders of infancy.

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17. Russetsky, J. J.: Ztschr. f. d. ges. Neurol. u. Psychiat. **89**:278-282, 1924.
18. Dupré and Merklen: Rev. neurol. **18**:1073-1074, 1909.
19. Heuyer, G., and Roudinesco, J.: Arch. de méd. d. enf. **39**:265-281, 1936.
20. Jacob, K.: Ztschr. f. d. ges. Neurol. u. Psychiat. **89**:458-491, 1924.
21. Krauss, S.: Schweiz. Arch. f. Neurol. u. Psychiat. **34**:94-124, 1934.
22. Hempel, J.: Ztschr. f. d. ges. Neurol. u. Psychiat. **165**:332-337, 1939.

There is little doubt that the stimulus sufficient to elicit a common reflex response is capable of activating an automatic dyskinesia ordinarily abortive in appearance. Apparently, the intensity of the stimulus may be of some importance. This would agree with the experience of Homburger,[23] who noted the appearance of usually absent athetoid finger movements with accelerated walking. Intermittent paroxysmal discharges of bilateral athetosis were precipitated by fast running in an adult studied by Scheibe.[24] His patient had had these attacks since the age of 5 years.

On the other hand, the accentuation of automatic dyskinetic phenomena by procedures of reflex stimulation constitutes a weighty argument against the acceptance of the reflex nature of the various motor phenomena described as reflex dyskinesia. One may theorize that some state of latency exists in such cases, with a threshold level that predetermines the strength of the stimuli required to initiate the motor reaction. The factors responsible for the suppression of the dyskinesia under basic conditions are unclear.

The fact remains that the dyskinetic phenomenon enters into the reflex situation so as to lead to the development of an entirely unique response. Its appearance is of the nature either of a foreign element or of a gross exaggeration, and even distortion, by comparison with the coexisting dyskinetic rudiments of the spontaneous variety. But, then, practically an identical situation exists in regard to motor changes typical of disturbances of the pyramidal order, and leading to gross alterations of the reflex status, often in the absence of any other visible criteria for the existence of a motor defect. While the reflex nature of the Babinski phenomenon has generally remained undisputed, it is important to note that this phenomenon is not a true reflex but the modification of a reflex or part of a more complex motor reaction. Its pathologic element lies essentially in the extensor response and in its tonic quality. This state of reflex alteration is explained by Goldstein[25] as the effect of a process of "dedifferentiation" that permits a more primitive type of movement to prevail. The same concept appears applicable to the understanding of reflex dyskinesias. The analogy between reflex reactions of the pyramidal and those of the extrapyramidal order seems to be valid and pertinent. Both pyramidal and extrapyramidal reflex reactions are modifications of reflex or motor processes by abnormal innervations or tonus distributions.

Of course, there are two more facts of importance for the understanding of the reactive quality of reflex dyskinesias: first, their manner of elicitation, which is the same as that in use for the routine testing of

23. Homburger: Arch. f. Psychiat. **69**:621-623, 1923.

24. Scheibe, H.: Arch. f. Psychiat. **114**:335-357, 1941.

25. Goldstein, K.: The Organism, Cincinnati, American Book Company, 1939.

the ordinary reflex phenomena, and, second, the intimate chronologic relation between stimulus and dyskinetic response. The motor effects thus obtained are varied and complex, yet conforming with the pattern of spontaneous dyskinetic reactions.

SUMMARY

The problem of overactivity in children has become confused by indiscriminate use of the term hyperkinesia. It is suggested that the designation of dyskinesia be reserved for special types of neuro-organic syndromes of extrapyramidal genesis.

While dyskinesias of automatic appearance are common and well studied, the reactive forms are rare and have received scant attention.

Three case studies of children with symptoms of reflex dyskinesia are presented, and the various patterns of reflex movement are described and analyzed. It is noteworthy that these movements are similar to spontaneous dyskinetic reactions but differ, both qualitatively and quantitatively, from the spontaneous motor activity seen in the same patient.

The coexistence of an abortive form of spontaneous dyskinesia, of manifestations of reflex dyskinesia, of synkinetic reactions of dyskinetic appearance and of hypertonus appears singular to the observations under discussion and is of distinct nosologic value.

The problem of the reflex nature of the reactive, or reflex, dyskinetic phenomena is discussed, both in the light of Goldstein's theory concerning pathologic alterations of reflex movements and from the pragmatic point of view.

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MESANTOIN[R] (METHYLPHENYLETHYL HYDANTOIN) IN TREATMENT OF EPILEPSY IN A STATE HOSPITAL

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MORE or less as the result of chance, bromides[1] and barbiturates[2] became known as useful drugs in the control of seizures. Good results in the treatment of patients with convulsive seizures were obtained with these two drugs and with fasting,[3] ketogenic[4] diet and dehydration.[5] However, there still remained a great number of patients who were not so benefited. Surgery and psychotherapy added to the number of patients whose seizures were brought under control.

In 1937, Putnam and Merritt[6] devised an experimental procedure which resulted in a striking acceleration in the development of additional drugs for use in the control of epileptic seizures. Their clinical report,[7] which followed shortly their laboratory studies, stimulated what later proved to be a justified enthusiasm for the use of diphenylhydantoin sodium U.S.P. (dilantin[R]). With the interest in this new drug went an intensive search for other drugs which would be of value in the control of seizures. There soon appeared reports on the use of ammonium chloride, azosulfamide,[8] brilliant vital red[9] and glutamic acid.[10]

From the Caro State Hospital for Epileptics; R. L. Dixon, Medical Superintendent.

1. Sieveking, E. H.: Analysis of Fifty-Two Cases of Epilepsy Observed by the Author, M. Tr. Roy. Med.-Chir. Soc. London **22**:157, 1857.

2. Hauptman, A.: Luminal bei Epilepsie, München. med. Wchnschr. **59**: 1907, 1912.

3. Geyelin, H. R.: Fasting as a Method of Treating Epilepsy, M. Rec. **99**: 1037, 1921.

4. Wilder, R. M.: The Effect of Ketonemia on the Course of Epilepsy, Proc. Staff Meet., Mayo Clin. **2**:307, 1921.

5. Gamble, J. L.: Dehydration, New England J. Med. **201**:909, 1929.

6. Putnam, T. J., and Merritt, H. H.: Experimental Determination of the Anti-Convulsant Properties of Some Phenyl Derivatives, Science **85**:525, 1937.

7. Merritt, H. H., and Putnam, T. J.: Sodium Diphenylhydantoinate in the Treatment of Convulsive Disorders, J. A. M. A. **111**:1068 (Sept. 17) 1938.

8. Cohen, M. E., and Cobb, S.: Anti-Convulsive Action of Neoprontosil in Epileptic Patients, Tr. Am. Neurol. A. **66**:199, 1940. Cohen, M. E.; Coombs, F. S.; Cobb, S., and Talbott, J. H.: Metabolic Studies on Epileptic Patients Receiving Azosulfamide and Phenobarbital, Arch. Neurol. & Psychiat. **50**:149 (Aug.) 1943.

The literature on diphenylhydantoin sodium accumulated at a rapid rate, and soon there appeared reports on the use of this drug in combination with others, particularly phenobarbital. There also were frequent references to untoward side effects.

However, the scientific methods introduced by Putnam and Merritt served these workers and others, in opening up new drugs to investigation. Such a drug is trimethadione (3,5,5-trimethyloxazolidine-2,4-dione; tridione[R]).[11] After reports on its anticonvulsant effects, Lennox[12] and DeJong[13] described its clinical effect in control of petit mal and psychomotor seizures. Merritt and Putnam[14] investigated the anticonvulsant properties of the sulfoxides and sulfones; Ellerman[15] reported his studies on the properties of 5,5-diphenyl-2,4-dioxo-thiazolidinedione (diphenylthiazolidinedione) and 5,5-diphenyl-2,4-dioxo-oxazolidinedione (epidon[R]). McQuarrie[16] and Aird[17] observed the effects of desoxycorticosterone on epilepsy. Fox and Tullidge[18] directed their studies toward the use of pyridoxine (vitamin B_6). Other reports appeared regarding 5-isophopoxymethyl-5-phenylhydantoin, sodium diphenylene hydantoin,[19]

9. Osgood, R., and Robinson, L. J.: Brilliant Vital Red As an Anti-Convulsant in Treatment of Epilepsy: A Study of Thirteen Cases, Arch. Neurol. & Psychiat. **40**:1178 (Dec.) 1938. Cobb, S.; Cohen, M. E., and Ney, J.: Anti-Convulsant Action of Vital Dyes, ibid. **40**:1156 (Dec.) 1938.

10. Price, J. C.; Waelsch, W., and Putnam, T. J.: *dl*-Glutamic Acid Hydrochloride in Treatment of Petit Mal and Psychomotor Seizures, J. A. M. A. **122**:1153 (Aug. 21) 1943. Waelsch, H., and Price, J. C.: Biochemical Aspects of Glutamic Acid Therapy for Epilepsy, Arch. Neurol. & Psychiat. **51**:393 (April) 1944.

11. Richards, R. K., and Everett, G. M.: Analgesic and Anti-Convulsive Properties of 3,5,5-Trimethyloxazolidine-2,4-Dione, Federation Proc. **3**:39 (March) 1944. Everett, G. M., and Richards, R. K.: Comparative Anticonvulsive Action of 3,5,5-Trimethyloxazolidine-2,4-Dione (Tridione), Dilantin and Phenobarbital, J. Pharmacol. & Exper. Therap. **81**:402, 1944.

12. Lennox, W. G.: The Petit Mal Epilepsies: Their Treatment with Tridione, J. A. M. A. **129**:1069 (Dec. 15) 1945.

13. DeJong, R. H.: The Effect of Tridione in the Control of Psychomotor Attacks, J. A. M. A. **130**:565 (March 2) 1946.

14. Merritt, H. H., and Putnam, T. J.: Anti-Convulsant Activity of Sulfoxides and Sulfones, Arch. Neurol. & Psychiat. **54**:319 (Nov.) 1945.

15. Ellerman, M.: Experimental and Clinical Studies on the Anticonvulsant Properties of Epidon, J. Nerv. & Ment. Dis. **106**:369 (Sept.) 1947.

16. McQuarrie, I.: Observations on the Therapeutic Effects of Desoxycorticosterone Acetate in Epilepsy, Am. J. Dis. Child. **72**:472 (Oct.) 1946.

17. Aird, R. B.: Effect of Desoxycorticosterone in Epilepsy, J. Nerv. & Ment. Dis. **99**:501 (May) 1944.

18. Fox, J. T., and Tullidge, G. M.: Pyridoxine (Vitamin B_6) in Epilepsy: A Clinical Trial, Lancet **2**:345 (Sept. 7) 1946.

19. Fabing, H. D.; Gayle, R. F., and Hawkins, J. R.: The Treatment of Epilepsy with Sodium Diphenylene Hydantoin, A. Research Nerv. & Ment. Dis., Proc. **26**:398, 1947.

dimethylethyl-oxazolidinedione and mesantoin[R] (3-methyl-5,5-phenylethylhydantoin).[20]

Tainter and others,[20] in 1943, after their study of the inhibition values of various drugs on convulsions, thus reported that methylphenylethyl hydantoin (mesantoin[R]) was similar to diphenylhydantoin in potency, with a dosage of approximately the same range. Loscalzo,[21] in 1945, reported favorably on the use of this drug in fixed combination with phenobarbital[22] in a small group of patients. He obtained a reduction of approximately 60 per cent in the incidence of seizures in his group. Those patients who failed to respond to diphenylhydantoin did not benefit from hydantal[R]. Although Tietz[23] did not direct her study toward the effect of this drug on incidence of seizures, some of the patients in her group did have convulsions, and her results indicated that, besides the reduction in incidence and severity of seizures, as reported by Loscalzo, there was a beneficial change in disturbances of behavior.

Clein,[24] also using hydantal[R], claimed that he obtained all the results of diphenylhydantoin, with none of its toxic effects. He reduced the dose of 1 patient who complained of being "woozy." Of 30 patients reported on by Lennox,[25] 20 per cent had far greater relief from methylphenylethyl hydantoin than from other drugs. He noted more frequent cutaneous reactions and greater sedation with this new drug but stated that there was absence of muscular incoordination and hyperplasia of the gums. In his series, patients with petit mal were not aided. Kozol[26] also claimed that petit mal failed to respond to this drug. His studies were made on 104 patients receiving the drug. Of this series, 60 per cent had an average monthly reduction of seizures of 90 per cent. His group was chosen mainly because of no response to maximum doses of diphenylhydantoin or because of unfavorable side effects. He reported drowsiness

20. Tainter, M. L., and others: Influence of Various Drugs on the Threshold of Electrical Convulsions, J. Pharmacol. & Exper. Therap. **79**:42 (Sept.) 1943.

21. Loscalzo, A. E.: Treatment of Epileptic Patients with a Combination of 3-Methyl-5,5-Phenylethyl Hydantoin and Phenobarbital: Preliminary Report, J. Nerv. & Ment. Dis. **101**:537 (June) 1945.

22. This combination in fixed relationship (phenobarbital, 0.02 Gm., and methylphenylethyl hydantoin, 0.1 Gm.) is called hydantal[R] by Sandoz Chemical Works, Inc.

23. Tietz, E. B.: The Use of Medicine in Behavior Disorders, M. Women's J. **53**:17 (Aug.) 1946.

24. Clein, N. W.: New Anti-Convulsant in the Treatment of Epilepsy, 3-Methyl-5, 5-Phenylethylhydantoin (Hylantal), Northwest Med. **44**:210 (July) 1945.

25. Lennox, W. G.: Newer Agents in the Treatment of Epilepsy, J. Pediat. **29**:356 (Sept.) 1946.

26. Kozol, H. L.: Epilepsy; Treatment with New Drug: 3-Methyl-5, 5-Phenyl-Ethyl-Hydantoin (Phenantoin), Am. J. Psychiat. **103**:154 (Sept.) 1946.

as a principal drawback to use of the drug and advised slow attainment of the maximum dose to obviate this side effect. One assumes that he would not encourage its use in combination with phenobarbital. Among its advantages, he listed the absence of any disagreeable taste (it can be taken in tablet form), gastric distress, hypertrophy of the gums or promotion of growth of hair. He reported appearance of a rash in 10 per cent of the patients. Of special interest is his mention of a 17 year old patient weighing 150 pounds (77.1 Kg.) who ingested 7.2 Gm. (72 tablets) in one dose, with only temporary deep stupor resulting. There is variance of opinion as to the dose necessary to obtain a therapeutic effect. Reports of several investigators indicate that the dose may vary from 0.1 to 1.0 Gm. for a given patient.

MATERIALS AND METHODS

In this study, we hoped to evaluate the effects of methylphenylethyl hydantoin on institutionalized epileptic patients. From a total patient population of 1,370, the original group of 26 patients was chosen. One (case 26) was adolescent. All the others were adult. Two (cases 24 and 26) were male. In the selection of these patients, no effort was made to exclude either idiopathic or symptomatic epilepsy from consideration, and both types were represented. All patients presented grand mal seizures. No patients with petit mal or psychomotor seizures were represented. The 26 patients were distributed as follows:

Group A: Fifteen patients representing the most extreme hypertrophy of the gums, as of Jan. 1, 1947. Fourteen had never achieved satisfactory control of seizures with diphenylhydantoin and/or phenobarbital, even in doses which caused the severe hypertrophy of the gums.

Group B: Six patients who had demonstrated what appeared to be practically no response to previous medication with diphenylhydantoin. Three had moderate hypertrophy of the gums and no obvious reduction in incidence of seizures.

Group C: The 4 surviving siblings of a family group of which 5 members were known to have myoclonus epilepsy of Unverricht. They were members of a family of 15 children. Their seizures were incompletely controlled by various other medicaments. All previous reductions in incidence of seizures by means of diphenylhydantoin or phenobarbital resulted in increased frequency and amplitude of the more incapacitating myoclonus.

Group D: One patient who had been without medication for the six years immediately preceding the study, because of persistent toxic reactions to all previous forms of medication.

For purposes of comparison, the following intervals of seizure incidence were used:

1. A period before any form of medication had been administered, and for which annual totals were available from our own records. These totals were used to obtain a monthly average of seizure incidence.

2. A pretest interval, during which the patients had received one or more forms of medication, either simultaneously or separately. All patients were re-

ceiving their maximum tolerated dose of diphenylhydantoin, with or without phenobarbital, except for patient 16, in group D, and patient 26, in group C. The latter was receiving 0.9 Gm. of trimethadione daily. This patient had a history of only a six month period of premedication and a six month period of trimethadione therapy. For all other patients there was a two to seven year interval during which they were receiving various forms of medication.

3. The period of methylphenylethyl hydantoin medication, Jan. 1, 1947 to Dec. 31, 1947. As the initial dose of the drug was gradually increased, the dose of other anticonvulsants was gradually decreased. The increase for groups A and D was usually a weekly increment of 0.05 Gm. daily. The dose for groups B and C was usually increased 0.1 Gm. daily at intervals of two to three weeks.

The data for comparison of the seizure incidences for each patient during the various periods are presented under the following heads:

1. "High." This figure represents the highest monthly total of seizures for the interval and the patient in question.

2. "Average." This figure represents the average of monthly totals for the year and the patient in question. When the incidence of seizures tended to decrease progressively, the totals for the first few months prevented the monthly average for the year from demonstrating the full drop in seizure incidence.

3. "Low." This figure represents the lowest monthly total obtained while the patient was under the medication in question.

4. "Low months." This figure represents the number of months in a single calendar year during which the low monthly total was obtained. Because the optimum dose of methylphenylethyl hydantoin was not obtained for several months of the test period, the months with the low totals were usually limited to the last half of the twelve month trial period.

The seizure control during medication with methylphenylethyl hydantoin is indicated in table 1, and comparative figures indicate the relative seizure incidences for periods of no medication and for periods of other medication. Also indicated is the development of undesirable side effects. The subsequent change of or reduction in medication is also indicated in this table.

RESULTS

If one accepts totals and percentages without qualification, one finds that the annual seizure totals for the four groups, with previous medication and with methylphenylethyl hydantoin medication, are 1,209 and 2,607, respectively, for group A; 1,531 and 1,512 for group B; 333 and 487 for group C, and 121 and 64 for group D. In only two groups was there a reduction for the year when the patients were receiving methylphenylethyl hydantoin. Group B shows a reduction of 19 seizures for a total of 72 patient months, and group D (a single patient group), a reduction of approximately 50 per cent in incidence of seizures.

Further enlightenment is given by comparing these periods for each individual patient. Five patients in group A, or 33 per cent, had a drop in the seizure total for the year. In group B, 50 per cent of the patients shared in reduction of the seizure total. Two, or 50 per cent, of group

TABLE 1.—*Comparative Figures on Incidence of Seizures for Periods Before and During the Administration of Mesantoin*

Group and Patient No.		Monthly Average Before Any Medication	Previous Medication, Daily Dose of Diphenylhydantoin Sodium and/or Other Substances	Monthly Seizures During Previous Medication				Monthly Seizures During Mesantoin[R] Medication				Maximum Dose of Mesantoin[R] Attained Daily	Toxic or Unfavorable Side Effects	Final Dose of Mesantoin[R] and/or Other Substances
				High	Average	Low	Low Months	High	Average	Low	Low Months			
A	1	17	0.3 Gm.	10	3.5	0	1	6	1	0	7	0.6 Gm.		0.6 Gm.
	2	8	0.4 Gm.	10	3.5	0	2	15	4	0	2	0.9 Gm.	Fever, numbness in March	0.9 Gm.
	3	33	0.3 Gm.; phenobarbital, 0.2 Gm.	56	31	5	1	75	20	0	6	0.8 Gm.	Dulness, stupor; ataxia	0.4 Gm.; amphetamine, 15 mg.
	4	10	0.2 Gm.; phenobarbital, 0.1 Gm.	9	3.5	1	2	6	2	0	5	0.9 Gm.		0.9 Gm.
	5	1.7	0.4 Gm.; phenobarbital, 0.1 Gm.	23	11	0	2	94	5.2	11	1	1.0 Gm.	Restlessness, nervousness; ataxia	0.3 Gm.; phenobarbital, 0.2 Gm.
	6		0.3 Gm.	12	2	0	9	23	5	0	5	0.5 Gm.		Diphenylhydantoin sodium 0.3 Gm.
	7	1	0.3 Gm.; phenobarbital, 0.2 Gm.	5	.3	0	11	2	0.15	0	11	0.4 Gm.		0.4 Gm.
	8		0.3 Gm.; phenobarbital, 0.2 Gm.	27	3	0	8	6	1	0	4	0.7 Gm.; phenobarbital, 0.065 Gm.		0.7 Gm.
	9		0.3 Gm.; phenobarbital, 0.1 Gm.	21	8	2	1	24	10.5	2	1	0.8 Gm.		0.8 Gm.

TABLE 1.—*Comparative Figures on Incidence of Seizures for Periods Before and During the Administration of Mesantoin—Continued*

Group and Patient No.		Monthly Average Before Any Medication	Previous Medication, Daily Dose of Diphenylhydantoin Sodium and/or Other Substances	Monthly Seizures During Previous Medication				Monthly Seizures During Mesantoin[R] Medication				Maximum Dose of Mesantoin[R] Attained Daily	Toxic or Unfavorable Side Effects	Final Dose of Mesantoin[R] and/or Other Substances
				High	Average	Low	Low Months	High	Average	Low	Low Months			
A	10		0.2 Gm.; phenobarbital, 0.2 Gm.	25	7.8	1	1	18	11	0	1	0.9 Gm.	Drowsiness	0.7 Gm.; amphetamine, 15 mg.
	11		0.2 Gm.	3	1.1	0	7	9	1.8	0	6	0.4 Gm.	Fever, rash in January, drowsiness	0.3 Gm. amphetamine, 15 mg.
	12		0.2 Gm.; phenobarbital, 0.3 Gm., amphetamine, 10 mg.	30	16	0	1	192	60.5	15	1	1.0 Gm.; phenobarbital, 0.1 Gm.		1 Gm. phenobarbital, 0.1 Gm.
	13		0.3 Gm.; phenobarbital, 0.2 Gm.	39	15	4	2	74	30	7	1	0.9 Gm.; phenobarbital, 0.1 Gm.	Loss in weight in February	0.9 Gm.; phenobarbital, 0.1 Gm.
	14		0.3 Gm.; phenobarbital, 0.1 Gm., amphetamine, 10 mg.	7	2.5	0	3	15	7.3	4	1	0.9 Gm.		0.9 Gm.
	15		0.3 Gm.	6	1.5	0	6	22	2.5	0	6	0.7 Gm.		0.7 Gm.
B	17	19	0.3 Gm.	29	17	7	1	47	35	22	1	0.4 Gm.	Mental disturbance with 0.3 Gm. of mesantoin[R]	Diphenylhydantoin sodium, 0.3 Gm.
	18		0.3 Gm.	36	22.5	10	1	129	37.5	4	1	1 Gm.	Drowsiness with 0.1 Gm. of mesantoin[R]	0.5 Gm.
	19		0.3 Gm.	15	7	3	1	22	4.5	0	3	1 Gm.		1 Gm.
	20	1.5	0.3 Gm.	77	35	6	1	63	25	2	1	1.1 Gm.	Dizziness, drowsiness, ataxia with 1.1 Gm. of mesantoin[R]	0.9 Gm.

Group and Patient No.		Monthly Average Before Any Medication	Previous Medication. Daily Dose of Diphenylhydantoin Sodium and/or Other Substances	Monthly Seizures During Previous Medication				Monthly Seizures During Mesantoin[R] Medication				Maximum Dose of Mesantoin[R] Attained Daily	Toxic or Unfavorable Side Effects	Final Dose of Mesantoin[R] and/or Other Substances
				High	Average	Low	Low Months	High	Average	Low	Low Months			
B	21		0.3 Gm.	27	10	2	1	30	9.5	0	4	0.9 Gm.	Drowsiness with 0.3 Gm. of mesantoin[R]	0.4 Gm.
	22		0.3 Gm.	16	12	5	1	34	15.5	0	1	0.6 Gm.	Headache, numbness with 0.5 Gm. of mesantoin[R]	None
C	23		0.3 Gm.; phenobarbital, 0.1 Gm.	12	1.5	0	7	33	9.5	1	1	1.1 Gm.; phenobarbital, 0.065 Gm.	Myoclonus increased in frequency and amplitude	None
	24		phenobarbital, 0.13 Gm.	14	20	0	7	58	16	1	1	1 Gm.		0.4 Gm.
	25		0.3 Gm.; phenobarbital, 0.1 Gm.	5	2	0	6	11	3	0	1	1 Gm.		None
	26	15	Trimethadione, 0.9 Gm.	35	14.5	7	2	23	13	4	1	1.1 Gm.		0.3 Gm.
D	16	4.5	0.3 Gm.		3.5			14	5.5	0	1	0.5 Gm.		0.5 Gm.

C showed such slight reductions as to be of no significance. In all, 11 (42 per cent) showed some reduction in seizure totals, the reduction for these 11 patients totaling 58.6 per cent; but this value is offset to such an extent by the gain in seizure incidence of the others that an increase of 46.21 per cent for all four groups (3,194 seizures, as compared with 4,670 seizures) results.

Closer scrutiny reveals that even such a presentation as that in table 1 fails to set forth all the cases in their true light. Therefore, table 2, for groups A and D, and table 3, for groups B and C, are presented to show the monthly totals of each patient's seizures for a calendar year with previous medication and with methylphenylthyl hydantoin. The numbers associated with some monthly totals indicate the number of 0.1 Gm. tablets daily attained at that time.

Thus, one can safely say from the data in table 2 that 8 of 16 patients have definitely shown a favorable response to methylphenylethyl hydantoin by a further reduction in incidence of seizures over that obtained with other medication, particularly diphenylhydantoin. Seven appear to have been adversely affected, and 1 patient did as well with one drug as with another.

Examination of table 3 (group B) reveals that 2 patients (cases 19 and 20) can be expected to continue to show better results with methylphenylethyl hydantoin than with diphenylhydantoin. The drop in seizure incidence in the midyear for patients 21 and 22 coincided with the administration of diphenylhydentoin, 0.3 Gm. daily, along with the methylphenylethyl hydantoin. The incidence again rose with the withdrawal of the former. These 2 cases suggest an advantage in administering both drugs in some cases, as the figures for similar months, when the patients received diphenylhydantoin alone, failed to reveal such a low incidence.

No patient in group C benefited from methylphenylethyl hydantoin, except possibly patient 25, and she was much more incapacitated by her myoclonus than formerly. It is safe to say that, for these 4 patients at least, methylphenylethyl hydantoin was not of benefit in the treatment of the myoclonus epilepsy of Unverricht. Thus, of the 22 remaining patients, 10 demonstrated a reduction of seizures by the substitution of methylphenylethyl hydantoin for diphenylhydantoin, and 2 patients benefited by the addition of methylphenylethyl hydantoin to diphenylhydantoin. When the patients with myoclonus are excluded, approximately 50 per cent receiving methylphenylethyl hydantoin benefited by a reduction in incidence of seizures.

In addition, all but 1 patient of group A had complete clearing of hypertrophy of the gums, and in this patient the hypertrophy originally present was greatly reduced. The hypertrophy of the gums of the 3 patients of group B receded during medication with methylphenylethyl

TABLE 2.—*Monthly Seizure Totals for Each Patient in Groups A and D*

Group and Case No.			Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
A	1	1946*	3	4	2	3	2	0	5	4	3	2	0	3
		1947*	1	3	6	2	6† 0	0	0	0	0	0	0	0
	2	1946*	9	5	7	7	8	6	5	5	10	5	8	8
		1947*	7	7	15	3	6	7 3	8 3	0	1	2	9 1	0
	3	1946*	15	5	23	20	15	19	14	19	20	13	10	32
		1947*	75	69	64	6	18	8 3	0	0	0	0	0	4 0
	4	1946*	3	3	2	2	4	3	4	6	5	4	6	5
		1947*	5	6	4	4	7 2	0	8 3	0	1	0	9 0	0
	5	1946*	14	10	12	10	29	22	15	14	5	16	9	20
		1947*	18	124	94	92	65	37	9 51	10 3 21	56	31	21	11
	6	1946*	0	1	0	1	0	0	0	0	0	1	0	0
		1947*	0	0	0	0	0	11	2	8 23	0 7	1	2	6
	7	1946*	0	0	0	0	0	0	0	0	0	0	0	0
		1947*	0	0	4 0	0	2	0	0	0	0	0	0	0
	8	1946*	0	4	2	3	0	0	0	10	1	0	0	0
		1947*	1	6	0	1	6 1	0	2	1	1	0	7 0	1
	9	1946*	21	14	3	5	3	8	12	3	20	8	12	15
		1947*	10	24	20	17	7 18	7	8 7	11	4	7	2	7
	10	1946*	3	5	8	6	4	6	9	7	7	2	2	2
		1947*	16	12	6	18	8	6	8 17	9 12	1	9	4	0
	11	1946*	5	3	5	1	1	2	2	1	4	1	1	2
		1947*	2	9	3	3	3 0	2	4 3 2	0	0	0	0	0
	12	1946*	16	14	30	12	18	16	0	11	10	18	16	18
		1947*	15	31	124	112	46	67	68	10 22	46	67	21	30
	13	1946*	17	13	23	13	12	10	17	7	11	8	15	7
		1947*	20	74	62	38	24	20	30	9 27	21	13	7	43
	14	1946*	3	3	3	7	7	0	0	0	2	6	5	2
		1947*	7	9	15	6	12	5	6	9 9	5	5	4	2
	15	1946*	0	0	0	2	0	0	1	0	3	1	5	6
		1947*	22	2	1	5 2	6 0	7 1	0	0	0	0	1	0

TABLE 2.—*Monthly Seizure Totals for Each Patient in Groups A and D—Continued*

Group and Case No.			Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
D	16	1946*	9	13	7	11	7	8	9	10	12	7	20	8
		1947*	14	9	15	4	4	6	4 3	5	1	2	5 0	1

*The two rows of figures for each case indicate the monthly seizure totals for the two years 1946 and 1947.

†The superscript numerals indicate the number of 0.1 Gm. tablets daily attained at that time.

TABLE 3.—*Monthly Seizure Totals for Each Patient in Groups B and C*

Group and Case No.			Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
B	17	1946*	15	22	29	17	24	21	22	24	28	28	23	35
		1947*	37	43	32	4 0† 37	28	41	1 47	35	38	29	31	4 22
	18	1946*	21	18	31	21	24	20	20	10	15	17	28	14
		1947*	35	25	45	129	10	4	27	10 6	3 71	29	5 42	27
	19	1946*	10	9	8	11	7	9	8	11	7	8	9	5
		1947*	22	5	11	5 2	3	7 3	8	10 1	1	0	0	0
	20	1946*	40	71	54	39	77	64	57	52	47	40	42	54
		1947*	50	63	24	33	37	8 28	9 36	11 3	10 2	9 4	13	8
	21	1946*	19	8	12	9	9	8	10	6	6	9	10	7
		1947*	12	30	15	4	0	7 0	0	9 0	3 11	4 27	3	0
	22	1946*	11	9	12	14	14	11	15	15	10	16	12	13
		1947*	14	17	12	5 0 34	1 14	2 6	4 18	6 2	0	0 31	22	15
C	23	1946*	2	1	1	1	2	0	4	4	3	2	1	3
		1947*	7	10	6	5	11	8 10	9 9	10 3	11 1	10	13	9
	24	1946*	0	1	0	6	11	10	11	14	12	11	5	4
		1947*	51	10	12	10	1	8	11	10 18	3 58	3	2	8
	25	1946*	0	6	2	3	2	0	4	9	11	5	16	6
		1947*	11	4	0	3	4	7 3	8 0	10 2	0 1	3	3	2
	26	1946*		8	4	19	27	12	10	7	35	12	19	7
		1947*	23	18	11	12	7	9 8	10 14	11 7	0 4	3 11	17	13

*The two rows of figures for each case indicate the monthly seizure totals for the two years 1946 and 1947.

†The superscript numerals indicate the number of 0.1 Gm. tablets daily attained at that time.

hydantoin. The effective dose varied from 0.3 to 1.0 Gm. daily, and the specific dose appeared to depend on the individual patient. Toxic effects sometimes presented themselves when the dose was as low as 0.1 Gm., but usually were not evident until the dose had attained 0.7 Gm. or over. The side effects that appeared early often subsided with a reduction in dosage and did not reappear with later increases. The side effects that appeared with larger doses were not so easily eliminated and occasionally precluded further increases later. The side effects noted were numbness, dulness, ataxia, cutaneous rash, loss of weight, mental upset, dizziness, headache and drowsiness. The last symptom was the commonest and appeared in a number of patients not receiving phenobarbital. When present, it was frequently well controlled with small doses of amphetamine. The few patients who received phenobarbital in addition to the methylphenylethyl hydantoin failed to show drowsiness. In 2 cases phenobarbital was administered to overcome the nervousness complained of by the patient.

One patient whose seizures were not reduced displayed a notable improvement in her personality, so much so as to counterbalance the few additional monthly seizures resulting from the change from diphenylhydantoin to methylphenylethyl hydantoin.

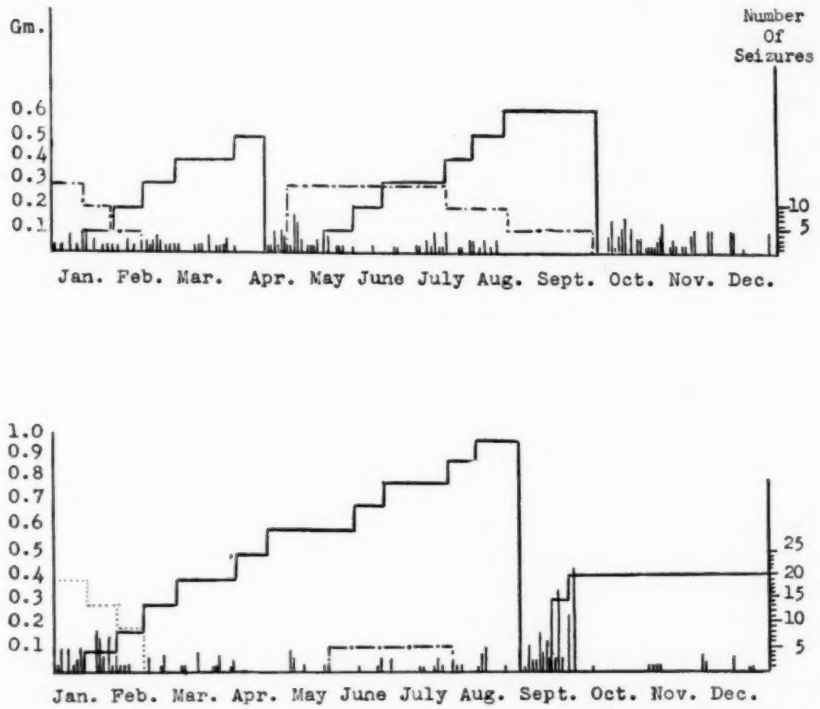
The side effects which my associates and I noted in a number of cases prompted us to discontinue the medication abruptly in several instances. In none of these cases did we encounter the development of status epilepticus. However, each patient who previously had exhibited some reduction in seizure incidence did experience a decided rise in frequency of seizures when the drug was abruptly discontinued. This increase in seizures continued for about twenty days. In a case in which we were not able to resume medication later, the patient returned to her seizure pattern prior to 1947. When the patient was later able to resume medication with methylphenylethyl hydantoin without further side effects, she again experienced a reduction in frequency of seizures. This can best be illustrated by the graph. Tables 1 and 3 would indicate that in case 22 (chart, upper graph) no reduction in seizures was derived from the administration of methylphenylethyl hydantoin. Examination of the chart indicates that for her the effective dose of the drug was 0.5 to 0.6 Gm., that she received this dose for only approximately two months of the year and that the resultant reduction in seizures was more than offset by the spurts of seizures each time she discontinued this drug. Case 24 (chart, lower graph) also demonstrates the effect of sudden cessation of the drug.

SUMMARY

A group of 26 institutionalized patients were given a one year trial of medication with mesantoin[R] (methylphenylethyl hydantoin). The

drug proved effective in reducing the frequency of seizures of 50 per cent of these patients, all but 1 of whom had previously failed to respond to diphenylhydantoin sodium. This anticonvulsant drug can also often be advantageously used in combination with diphenylhydantoin, even when either substance used alone is ineffective.

It should be possible to obtain still more striking results if methylphenylethyl hydantoin were used with a number of patients who also



Effect of sudden withdrawal of mesantoin[R] (methylphenylethyl hydantoin) on incidence of seizures. Upper graph, case 22; lower graph, case 24.

Values for methylphenylethyl hydantoin are shown by the solid line; those for diphenylhydantoin, by the line of dots and dashes, and those for phenobarbital, by the line of dots (each increment represents only 0.03 Gm.).

Seizures are indicated by the short vertical lines, the number of seizures being proportionate to the length of each line, and each line representing a single day.

respond well to other drugs. Except for the severe hypertrophy of the gums and diplopia caused by diphenylhydantoin in some patients, and not encountered in the use of methylphenylethyl hydantoin, the latter caused the same side effects as the former, namely, dizziness, muscular incoordination, ataxia, gastric discomfort, hyperirritability, restlessness, loss of weight, dermatitis and drowsiness. Drowsiness, rather than dermatitis, appears to be the commonest side effect resulting from the use of this drug.

Reduction in frequency of seizures and development of side effects appear to be dependent on the peculiarities of the individual patient, rather than on the general, absolute qualities or the dose of the drug. The effective dose differs with each patient and may vary from 0.3 to 1.0 Gm.

No incompatibility between methylphenylethyl hydantoin and phenobarbital was encountered, and the latter can often be used to overcome the restlessness and irritability occasionally caused by the former. Amphetamine was effective in overcoming the drowsiness caused by methylphenylethyl hydantoin in some cases. In our 4 cases of myoclonus epilepsy of Unverricht, methylphenylethyl hydantoin was contraindicated. In 1 case there was notable improvement in the patient's well-being, even though there was no reduction in the frequency of seizures. The results warrant the further use of this drug, either alone or in combination with other drugs. Greater personal attention to the individual patient can result in greater beneficial effects and fewer side effects.

APPENDIX

Since the completion of the foregoing studies, we have administered methylphenylethyl hydantoin to a number of additional patients. In most cases we continued to start the treatment with 0.05 to 0.1 Gm. daily and then very slowly increased the daily dose. Only in 1 case did we inadvertently begin with 0.3 Gm. In this case, ten days from the time the patient started to take the drug, while she was still receiving 0.3 Gm., a generalized rash developed. Because of the intense cutaneous reaction, followed by prostration and death, a separate report of this case has been made elsewhere.[27] However, we feel compelled to offer here a word of caution in the use of this drug and to suggest that in no circumstances should treatment be started with a dose of more than 0.1 Gm., that all increases in dosage be made in small increments, at a very slow pace, and that one should be particularly hesitant in administering the drug to a patient who has previously shown a strong tendency toward cutaneous reactions with the use of other drugs.

Caro State Hospital for Epileptics

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GLUCOSE TOLERANCE IN DISTURBED SCHIZOPHRENIC PATIENTS

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HOSKINS[1] pointed out that the presence of an abnormal response to the Exton-Rose glucose tolerance tests in a high proportion of schizophrenic patients has been repeatedly confirmed. He stated the belief that "elaborate theorizing" concerning the reasons for these observations "would hardly be profitable in the current stage of our ignorance of the actual mechanisms involved." Braceland, Meduna and Vaichulis[2] asserted that there is a delay in the action of insulin in these patients, probably due to the anti-insulin factor demonstrated by Meduna, Gerty and Urse.[3] Braceland and his associates observed that abnormal curves were found oftenest in cases of the acute disease, but were not related to the fasting blood sugar or to the type of schizophrenia. In 1922 Lorenz[4] found hyperglycemic responses to glucose feeding in catatonic and emotionally upset schizophrenic patients.

PRESENT INVESTIGATION

During the war, a group of acutely psychotic enlisted men of the Navy and Marine Corps were observed at the United States Public Health Service Hospital at Fort Worth, Texas. The psychoses of these men were characterized by a high rate of rapid recovery, as well as by a high incidence of extremely disturbed behavior in the early stage of their illnesses. The disturbed patients characteristically became progressively quieter, and by the end of three months were either well enough to be discharged into civilian life or had lapsed into a fairly typical chronic schizophrenic process, requiring further treatment at a veterans' hospital.

From the Students' Health Department, University of Minnesota, and the United States Public Health Service Hospital, Fort Worth, Texas.

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2. Braceland, F. J., Meduna, L. J., and Vaichulis, J. A.: Delayed Action of Insulin in Schizophrenia, Am. J. Psychiat. **102**:108-110 (July) 1945.

3. Meduna, L. J.; Gerty, F. J., and Urse, V. G.: Biochemical Disturbances in Mental Disorders: I. Anti-Insulin Effect of Blood in Cases of Schizophrenia, Arch. Neurol. & Psychiat. **47**:38-52 (June) 1942.

4. Lorenz, W. F.: Sugar Tolerance in Dementia Praecox and Other Mental Disorders, Arch. Neurol. & Psychiat. **8**:184-196 (Aug.) 1922.

It was thus possible to study the same patients in two stages of illness (acute psychosis and chronic psychosis, or acute psychosis and social recovery) within a relatively short period (average, two and one-half months). The chief objects of this experiment were to determine the consistency of the Exton-Rose response, i.e., to find out whether schizophrenic patients could be divided into two consistent groups on the basis of their glucose tolerance, and to study the relation to the prognosis of the response to the test. In addition, this experiment would, it was hoped, add evidence to support or to question previous observations concerning the relation of the curves to acute processes, to symptoms and to electric convulsive therapy.

One hundred and two patients were selected by the following criteria: Each week from the ward housing the 36 most disturbed patients of about 1,000 in the hospital, 3 to 5 new patients were chosen to whom the Exton-Rose one-hour, two-dose glucose tolerance test was administered. Repeat tests were obtained on 92 of this group approximately two and one-half months later. Second repeat tests were performed on 8 patients and a third set on 2 patients. In these tests a fasting sample of blood was drawn and 50 Gm. of glucose in water administered orally; thirty minutes later another sample of blood was drawn and another 50 Gm. of glucose administered, and thirty minutes after the second dose a third sample of blood was drawn. Blood glucose levels were determined by the method of Folin and Wu. Abnormal responses to the Exton-Rose test were recorded according to the criteria of Bodansky and Bodansky;[5] i.e., a test was scored as abnormal when the second reading was 75 mg. or more per hundred cubic centimeters above the first, or the third reading was more than 5 mg. per hundred cubic centimeters higher than the second. Otherwise, the test was scored as normal. All fasting blood sugars were within normal limits.

RESULTS.—The patients were divided into six groups, as follows:

Group	No. of Patients	Test	Response to Exton-Rose Test
1	30	First Second	Normal Normal
2	14	First Second	Normal Abnormal
3	17	First Second	Abnormal Normal
4	26	First Second	Abnormal Abnormal
5	5	These patients either demonstrated flat curves on initial testing (2 cases) and equivocal results on repeat testing (2 cases) or proved to be diabetic (1 case)	
6	10	Original	Abnormal (6) Normal (4) (The patients' departures from the hospital were so abrupt that no repeat testing could be performed)

The accompanying table presents statistics concerning the background, symptoms and outcome. The patients were given intensive "push" treatment, including occupational therapy, psychotherapy and, in about half the cases, electric convulsive therapy. Although the syndromes were

5. Bodansky, M., and Bodansky, O.: Biochemistry of Disease, New York, The Macmillan Company, 1940.

atypical in a large proportion of patients, all but 2 were considered to be suffering basically from a schizophrenic process. In 1 case in group 2 and in 1 case in group 4, trauma was the basis of the psychosis.

Ten of 12 control subjects (physicians) gave normal responses to the Exton-Rose test; 5 of the 10 were retested about three months later and again gave normal responses.

Although all patients were quartered in the ward for disturbed patients, some on the day of the test were relatively quiet. Of 41 relatively

*Data on Patients with Schizophrenia Classified According to Response to Exton-Rose Glucose Tolerance Test**

Groups	N-N 1	N-A 2	A-N 3	A-A 4	Irregular Responses 5	One Test 6	Initial Test	
							Normal	Abnormal
Cases	30	14	17	26	5	10	49	53
Average age, yr.	22.4	23.1	23.0	26.2	28.8	23.0	22.8	24.5
Broken homes, %	44	50	69	54	100	30	49	53
History of mental illness in family, %	22	23	59	13	60	50	27	35
Average no. of months of service before hospitalization	17½	12	18½	13½	27	10½	15	15½
History of combat, %	52	38	46	35	60	30	47	40
Acute onset, %	37	50	29	36	0	40	39	35
Average no. of months in hospital before first test	2.9	2.4	2.8	2.5	2.6	2.7	2.8	2.5
Symptoms								
Predominantly hebephrenic, %	33	21	6	15	40	20	31	12
Predominantly paranoid, %	40	36	53	38	60	30	39	42
Predominantly catatonic, %	23	36	35	31	0	40	27	34
Others, %	3	7	6	15	0	10	4	12
Electric convulsive therapy	53	43	71	38	40	44	51	49
Results Social recovery, %	67	57	59	50	100	56	63	57
Chronic, %	33	43	41	50	0	44	37	43

*N-N indicates a normal response to both the initial and the repeat glucose tolerance test; N-A, a normal response to the first and an abnormal response to the second test; A-N, an abnormal response to the first and a normal response to the second test; A-A, abnormal responses to both tests.

quiet subjects, 56 per cent had abnormal Exton-Rose curves; 39 per cent of 23 moderately disturbed and 53 per cent of 37 extremely disturbed subjects had abnormal curves. All patients had an opportunity to eat a balanced diet of adequate caloric content; some subjects, however, had been eating poorly with much persuasion (no patient who required tube

feeding was included). Nine (75 per cent) of 12 patients who presented feeding problems gave hyperglycemic responses to the Exton-Rose test; of 4 who had been eating ravenously, 2 gave abnormal and 2 normal responses.

Two patients in group 5 gave unusually perplexing results. Thus, the first test on patient 14 gave readings of 81, 94 and 377 mg. per hundred cubic centimeters; by the time (a week later) that the test could be repeated, in order to check on the accuracy of the third reading, the patient appeared to be greatly improved. His second test gave normal readings: 85, 111 and 73 mg. per hundred cubic centimeters. Four weeks later he had relapsed, and a third test gave readings of 79, 79 and 133 mg. per hundred cubic centimeters. A month after the third test, when he had again improved (and eventually could leave the hospital) his responses were abnormal (83, 141 and 174 mg. per hundred cubic centimeters).

The first test on patient 37 gave readings of 85, 141 and 102 mg. per hundred cubic centimeters; three months later, when, despite shock treatment, a chronic illness apparently was developing, his curve had become abnormal (75, 82 and 164 mg. per hundred cubic centimeters). This patient was not transferred and could be followed further; three months later he had improved so that he could be discharged, and his curve again became normal, although much flatter than before (70, 83 and 65 mg. per hundred cubic centimeters).

No significant average differences in fasting blood sugars were found between the subjects with abnormal and those with normal curves, between readings for the first and those for the second testing, between patients ready for discharge and those chronically ill, between those who ate an average amount and those who presented feeding problems or between those who were extremely disturbed at the time of examination and those who were relatively quiet.

COMMENT

1. Can schizophrenic patients be divided into two consistent groups according to their responses to the glucose tolerance test? Although the majority of the patients (groups 1 and 4) gave similar curves on retesting, over one third of all those tested twice showed a change. Particularly difficult to understand is group 2; of the 14 subjects, 8 showed normal Exton-Rose curves while acutely psychotic and abnormal curves two or three months later while apparently the psychosis was in remission. Although abnormal curves for the Exton-Rose glucose tolerance tests were more frequently encountered in schizophrenic patients than in control subjects, it cannot be assumed that the values shown in one testing are typical for a given patient.

2. Is the Exton-Rose test of value in prognosis? Subjects giving an initial normal response had a slightly higher rate of improvement, but the difference (63, as compared with 57, per cent) is too small to be significant. Follow-up studies on patients discharged from this hospital have shown that relapses are not infrequent, but there are no adequate criteria by which to predict which patients will relapse. Schizophrenia is such an insidious illness that, although the evidence from this work indicates that the test is not of prognostic value, long term follow-up studies would be required to establish this point.

3. Are abnormal responses to the Exton-Rose test more frequently found in combative, hyperactive ("disturbed") patients than in the average type of schizophrenic patients? Braceland, Meduna and Vaichulis[2] found that only 37 of 102 presumably average schizophrenic patients had normal curves; in this study, 49 of 102 disturbed patients had normal curves on the first test.

4. Are abnormal curves more frequently found among patients with more acute psychoses? In this series of patients (all of whom could be considered relatively acutely ill) there was no appreciable difference, as shown by the percentages of patients with acute onset and by the months of hospitalization before the first test. The patients studied by Braceland and associates,[2] who presumably had more "chronic" illnesses, had less frequent normal curves than did the present series of patients with more acute psychoses.

5. Are symptoms related to the findings in the Exton-Rose test? The patients with predominantly hebephrenic symptoms seemed more likely to have normal curves, whereas a majority of those with catatonic symptoms had abnormal curves. Since there were few typical examples of any of the subgroups of schizophrenia and much overlapping, conclusions concerning symptoms must be viewed conservatively. The intensity of disturbed behavior on the day of testing apparently was not related to the results of the test.

6. How are glucose tolerance curves affected by electric convulsive therapy? Twenty-two patients with normal curves were treated by this means; 6 of these later showed abnormal curves. Of 22 subjects with abnormal curves so treated, 12 later showed normal curves. There is, thus, a suggestion that electric convulsive therapy may tend to retain or to produce normal curves. With such small groups, however, and with the obscurity of the basis for the abnormal and normal curves, this finding may well be attributable to chance, as may the high incidence of familial mental illness in group 3.

SUMMARY

1. About one-half of 102 acutely disturbed schizophrenic patients gave abnormal responses to the Exton-Rose glucose tolerance test. This is a much higher incidence than has been reported for nonpsychotic, control, subjects.

2. The Exton-Rose curve was not of value in predicting whether a patient would still be psychotic or his psychosis would be in a remission after two or three months.

3. Retests after two or three months showed inconsistencies in response: Of the group whose first Exton-Rose curves were abnormal, two thirds continued to give abnormal responses, but one third had normal curves; of the group whose first curves were normal, two thirds continued to give normal responses, but those of one third became abnormal. Alterations in response to the test did not correspond to alterations in clinical course.

4. There were no clearcut relations between glucose tolerance curves and acuteness of the illness, or electric convulsive therapy.

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ABSCESS OF BRAIN DUE TO CLOSTRIDIUM PERFRINGENS TREATED WITH PENICILLIN

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EARLY in 1945, a patient with a fulminating infection of the brain due to Clostridium perfringens (gas bacillus) following a depressed fracture of the frontal lobe was treated with penicillin and recovered. It was expected that many such cases of craniocerebral wounds due to war injuries would be encountered and reported. However, only 1 case of cerebral abscess due to this bacillus has appeared in the literature since that time. It was thought justifiable, therefore, to record this case.

The case described here, encountered in civilian practice, was one of a compound, depressed fracture of the left frontal bone complicated by a large abscess of the frontal lobe, from which Cl. perfringens was cultured. It is unique in that, owing to a gross oversight on the part of the attending physicians, gas gangrene antitoxin was not given. The patient was found to be sensitive to the sulfonamide drugs, and so the treatment consisted entirely of surgical drainage and administration of penicillin. The efficiency of the treatment in combating an otherwise fatal infection was demonstrated by a complete clinical recovery.

REPORT OF A CASE

P. B., a Puerto Rican aged 49, was admitted to the St. Francis Hospital on Jan. 25, 1945, in an unconscious condition. The history obtained from his wife was that on January 19 the patient had fallen while drunk, striking the left side of his forehead on a broken bottle. A small wound in the scalp had been closed at the emergency hospital and the patient sent home.

The patient's wife stated that two days after the injury he had begun to have difficulty with his speech, being unable to express himself. He complained bitterly of headache, and the following day he became drowsy, listless and feverish.

On the sixth day after injury he was removed to the hospital in a semi-stuporous state. He could be aroused but was unable to talk. The temperature was 99 F. and reached 101 F. the following day. The white blood cell count was 6,800, with 74 per cent polymorphonuclear leukocytes. The wound in the scalp was open and edematous and oozed frothy, creamy pus. The patient's neck was stiff. Lumbar puncture revealed light yellow, turbid fluid, containing 200 cells per cubic millimeter, mostly lymphocytes, and gram-positive organisms were found on smear. The culture revealed Staphylococcus aureus.

The patient was placed under treatment with sulfadiazine, 1 Gm. being given every four hours. Twelve hours later the urine was grossly bloody, with a 2 plus reaction for albumin and numerous sulfonamide crystals. The sulfadiazine was therefore discontinued, and penicillin therapy was begun, 20,000 units being given intramuscularly every three hours. By the evening of the second day after his admission to the hospital, the patient's coma had deepened; he was incontinent of urine and feces, and the temperature had risen to 102 F. I was then called in consultation.

If the roentgenograms of the skull, which were taken on his admission to the hospital, had been properly interpreted, neurosurgical consultation would probably have been sought earlier. The lateral exposure disclosed a depressed fracture of the left frontal bone, with fragments of bone penetrating the intracranial cavity to a depth of 2 cm. (fig. 1). A fairly extensive collection of gas could be seen filling the left frontal lobe over an area 4 by 6 cm. The gas was first thought to have entered by way of the frontal sinus; but, since the line of

Fig. 1.—Roentgenograms of the skull taken on the patient's admission, six days after injury. Note the depressed bone surrounded by air. The anteroposterior view is reversed.

fracture did not enter any of the paranasal sinuses, it was obviously of bacterial origin.

Treatment and Subsequent Course.—At operation, a small scalp flap was turned down about the wound on the left side of the forehead. The injury to the skull presented as a small linear fracture line 3 mm. wide and 3 cm. long. This small, innocent-appearing opening in the outer table of the skull was a camouflage for the extensive injury beneath and was probably responsible for the minor treatment given at the time of the injury.

A single trephine hole was enlarged with a ronguer. Several large pieces of the inner table of the skull had been broken and embedded deeply in the frontal lobe. The dura mater was extensively lacerated and covered with purulent granulation tissue. On removal of the largest fragment of bone, a large abscess was entered, containing nearly 40 cc. of foul-smelling, greenish yellow, frothy pus. After the purulent material had been washed out, the abscess cavity measured 4.5 cm. in diameter!

The principal organism recovered from the pus by both smear and culture was a gram-positive, anaerobic bacillus with the cultural characteristics of Cl. perfringens.

In the surgical treatment of this abscess, the method used by Comdr. Exum B. Walker, at that time neurosurgeon to the Aiea Naval Hospital, was followed. Dr. Walker had had numerous war casualties whose cerebral abscesses he had treated with an open drainage, the defect in the skull being covered by a tantalum plate and the wound closed tightly except for a small catheter in one corner of the wound for the injection of penicillin. This method was later described by Gardner.[1] The healing by primary intention of these traumatic abscesses of the

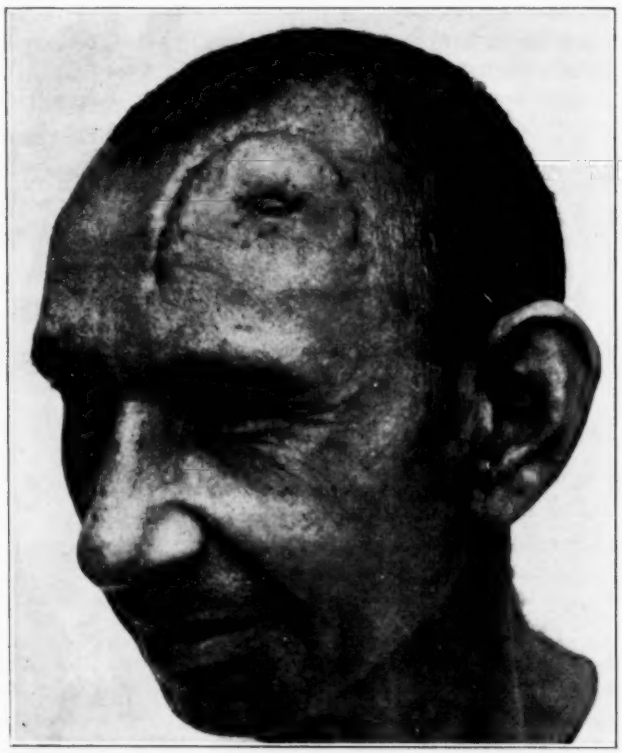

Fig. 2.—Photograph of patient on discharge, five weeks after injury.

brain was remarkable. In treatment of this patient, therefore, a small tantalum plate was fashioned to cover the defect, and the scalp was closed tightly, a small rubber catheter being left in one corner of the wound.

The patient responded immediately to the surgical treatment; the following morning he was conscious, taking food and fluids by mouth, but was aphasic. A dose of 60,000 units of penicillin in divided doses was injected into the abscess cavity through the catheter in the next two days, before the tube was removed; 20,000 units of penicillin was given intramuscularly every two hours.

For the next seven days, the patient showed little improvement. The temperature ranged in a septic fashion from 100 to 102 F. daily, the pulse rate remain-

1. Gardner, J.: Use of Tantalum for Repair of Cranial Defects in Infected Cases, Cleveland Clin. Quart. **13**:72-87 (April) 1946.

ing about 60 to 64 per minute. He was conscious, took food and fluids well but was listless and incontinent. There were no signs of paralysis, but the complete aphasia continued. On the eighth postoperative day the wound appeared swollen and boggy; and, because of the continued fever, the patient was again taken to the operating room and the wound reopened. When the tantalum plate was removed, the large, 4.5 cm., cavity of the abscess was observed to have filled in with edematous brain tissue. On exploring the area, several small pockets of creamy, purulent material were encountered. Cultures of pus from these pockets, however, gave no growth of organisms. In an effort to open all these small pockets, the frontal horn of the lateral ventricle was opened and a sudden gush of xanthochromic cerebrospinal fluid resulted. The tantalum plate was not replaced, and the wound was again closed with the catheter in place as before.

There was immediate response to the second surgical procedure. The patient's temperature was normal within thirty-six hours and remained so until his discharge. A total of 35,000 units of penicillin was injected into the area of the abscess in three separate doses, and the catheter was removed. Because of the difficulty in obtaining penicillin, he was given only 10,000 units every three hours after the second operation; this dosage was continued for thirteen days. During the patient's twenty-seven days in the hospital, he received a total of 2,385,000 units of penicillin, 2,290,000 of which were given intramuscularly and 95,000 injected directly into the abscess cavity.

The patient showed steady improvement after the second operation. The wound healed completely in four days. The aphasia rapidly cleared, so that by the time he was discharged from the hospital he could converse, with only occasional hesitation on a word. A photograph of the patient taken on his discharge from the hospital is shown in figure 2.

The patient returned to work six weeks after his discharge from the hospital, during which time he gained 12 pounds (5.4 Kg.) in weight, and has remained in excellent health up to the present time. On June 15, 1945, he was readmitted to the hospital, where encephalograms revealed extensive dilatation of the anterior horn of the lateral ventricle. After the encephalographic study, a tantalum plate was inserted to cover the disfiguring depression in the frontal bone.

COMMENT

It is incredible that the gas bacillus, which causes such havoc when attacking other parts of the body, would be so innocuous in the brain. The patient showed no other signs of illness except those of intracranial pressure and the aphesia due to the local involvement of the brain. The temperature was never over 102 F. Whether this relatively benign clinical course should be attributed to the effect of the penicillin or to the low virulence of the organism attacking the brain, one cannot say. The use of penicillin alone could not have resulted in the patient's recovery. Surgical drainage of the abscess was necessary. It was discovered later that the patient had not been given the routine injection of gas gangrene antitoxin U.S.P. Each of four doctors who had treated him had thought one of the others had given him the antitoxin. The sulfonamide drug was withdrawn after the initial dose of 4 Gm. because of immediate hematuria. Roentgen therapy, sometimes used in the treatment of gas bacillus infections, was not given.

We were aware of the report of Walker on the harmful effects of injecting penicillin into the ventricular system. Even though there was a direct communication between the ventricle and the abscess cavity, no untoward symptoms appeared after penicillin was instilled through the catheter into the abscess.

REVIEW OF LITERATURE

The bacteriostatic effect of penicillin in controlling the spread of infection due to the gas bacillus was early recognized experimentally by McIntosh and Selbie,[2] and later by Hac and Hubert.[3] These authors, using penicillin to protect mice against infection with Cl. perfringens, concluded that penicillin was far superior to proflavine sulfate, the sulfonamide compounds or any other therapeutic agent heretofore employed for this infection. The first report, by Keefer,[4] of the National Research Council on treatment of infections with penicillin, stated that "experimentally penicillin is a potent agent in gas infections, but up to the present time there are no studies in human cases."

Sporadic reports began to appear in the literature early in 1944 demonstrating the clinical value of penicillin in treating gas bacillus infections. Since that time, many articles have been published reporting gas bacillus infections in all parts of the body treated with penicillin parenterally and locally, with almost miraculous recoveries. McKnight, Loewenberg and Wright;[5] Kepl, Ochsner and Dixon;[6] Wood, Holtzman, Goodyear and Rich;[7] Pickett,[8] and others have reported gas bacillus infections of extremities following compound fractures. Hudson and Rucker[9] reported a case of gas bacillus infection of the uterus treated

2. McIntosh, J., and Selbie, F. R.: Zinc Peroxide, Proflavine and Penicillin in Experimental Clostridium Welchii Infections, Lancet **2**:750-752 (Dec.) 1942.

3. Hac, L. R., and Hubert, A. C.: Experimental Clostridium Welchii Infection: Local Sulfonamide Therapy (Sulfadiazine, Sulfathiazole, Sulfanilamide), J. Infect. Dis. **74**:150-160 (March-April) 1944.

4. Keefer, C. S.: Penicillin in the Treatment of Infections: A Report of Five Hundred Cases, J. A. M. A. **122**:1218-1224 (Aug. 28) 1943.

5. McKnight, W. B.; Loewenberg, R. D., and Wright, V. L.: Penicillin in Gas Gangrene, J.A.M.A. **124**:360 (Feb. 5) 1944.

6. Kepl, M.; Ochsner, A., and Dixon, J. L.: Two Cases of Clostridium Welchii Infection Treated with Penicillin, J.A.M.A. **126**:96-98 (Sept. 9) 1944.

7. Wood, W. S.; Holtzman, S.; Goodyear, A. F., and Rich, C.: Gas Gangrene Treated with Penicillin, Illinois M. J. **87**:145-146 (March) 1945.

8. Pickett, W. J.: Penicillin in Gas Gangrene, Illinois M. J. **87**:29-31 (Jan.) 1945.

9. Hudson, G. S., and Rucker, M. P.: Gas Bacillus Infection of Uterus Treated with Penicillin, Illinois M. J. **87**:145-146 (March) 1945.

with penicillin. Meleney, Friedman and Harvey[10] described a case of infection of the abdominal wall. Harris and Leviton[11] reported a case of infection of the scrotum and foot with the gas bacillus. All the patients recovered.

The value of penicillin as a prophylactic agent in the development of gas bacillus infections complicating traumatic wounds was demonstrated by Fisher, Florey, Grimson and Williams,[12] who reviewed 4,000 battle casualties. Of the wounded who did not receive penicillin, 0.81 per cent became infected with the gas bacillus. Jeffrey and Thompson[13] and Cutler and Sandusky[14] also demonstrated the value of penicillin as an agent in preventing the development of gas bacillus infection.

The occurrence of an abscess in the brain due to the gas bacillus is relatively rare in civilian practice. A careful search of the entire literature has revealed only 6 cases. Dandy,[15] in 1927, reported a case of pneumocephalus of bacterial origin following trauma. A well defined abscess containing gas was evacuated, but Cl. perfringens was not accurately identified. He reviewed a case of Bier's and 2 of Rychlik's in which gas-forming organisms (Cl. perfringens) had produced cerebral abscesses. Bier's case was too sketchily described to permit definite conclusions, but it seemed that in Dandy's case and the 2 cases of Rychlik the abscesses were due to gas-forming bacilli. Lovering and Craig[16] reported the case of a 4 year old boy who had been kicked in the head by a horse. A compound fracture of the skull was followed by an abscess in the frontal lobe, from which Cl. perfringens was obtained. Treatment consisted in irrigating the wound with hydrogen peroxide, application of sulfathiazole powder locally and administration of the drug by mouth and intravenously, injection of gas gangrene antitoxin every four days and roentgen therapy. A delayed removal of the fragments of bone from the frontal lobe was followed by growth of a cerebral fungus, which was later removed. The boy recovered after a stormy course of six weeks.

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10. Meleney, F. L.; Friedman, S. T., and Harvey, H. D.: The Treatment of Progressive Bacterial Synergistic Gangrene with Penicillin, Surgery **18**:423-434 (Oct.) 1945.

11. Harris, C. M., and Leviton, L. R.: Penicillin Treatment of Gas Gangrene of Scrotum and Foot, Am. J. Surg. **69**:391-396 (Sept.) 1945.

12. Fisher, G. H.; Florey, M. E.; Grimson, T. A., and Williams, P. M.: Penicillin in Clostridial Infections, Lancet **1**:395-399 (March 31) 1945.

13. Jeffrey, J. S., and Thompson, S.: Gas Gangrene in Italy: A Study of Thirty-Three Cases Treated with Penicillin, Brit. J. Surg. **32**:150-167 (July) 1944.

14. Cutler, E. C., and Sandusky, W. R.: Treatment of Clostridial Infection with Penicillin, Brit. J. Surg. **32**:168-176 (July) 1944.

15. Dandy, W. E.: Pneumocephalus of Bacterial Origin, Arch. Surg. **15**:913-917 (Dec.) 1927.

Otenasek and Chalmers[17] have recently reported a case of fulminating gas gangrene of the brain. Although the patient was treated surgically and all forms of chemotherapy were administered, death occurred in seventy-two hours after injury. Autopsy revealed massive necrosis of the right cerebral hemisphere, with bubbles of gas throughout the entire brain. These authors emphasized the distinction between gas gangrene and so-called anaerobic cellulitis of the brain. They stated that gas gangrene should be reserved for the infection characterized by severe toxemia and massive edema of tissue with necrosis, in the presence of anaerobic gas-forming organisms. The term anaerobic cellulitis can be applied to those cases in which an active infection with gas-forming anaerobes is present but not gangrene. The virulence of the organism and the resistance of the patient to it are probably responsible for these two clinical pictures.

Pathologically, in the majority of cases, the cerebral abscesses due to Cl. perfringens remain localized and are walled off by the brain in a manner similar to that of other invading organisms. This had occurred in the cases described and cited by Dandy, Lovering and Craig and in the case reported here. It has long been the impression of pathologists that the multiple abscess of the brain due to the gas bacillus frequently observed in postmortem specimens is due primarily to the unbridled growth of the bacillus and extension of the infection after death. The extensive infection of the brain by the gas bacillus in the case of Otenasek and Chalmers may have been postmortem invasion of the organism.

The contamination of war wounds of the brain with the gas-producing organisms is probably much commoner than the scarcity of reports in the English medical literature would indicate. Early in the war a committee of Soviet scientists[18] studied the bacteriology of penetrating craniocerebral wounds. Of 300 wounds, only 2 were sterile. Sixty-one per cent were contaminated with cocci; 20.5 per cent, with putrefactive anaerobes, and 11.2 per cent, with gas-forming organisms, of which 94 per cent were infections with Cl. perfringens. The highest mortality occurred with infections of the latest type; 50 per cent of the patients died regardless of therapy. At the time of this report only the sulfonamide drugs were available for chemotherapy of these wounds. In the last year of the war, the unlimited supply of penicillin to the armed forces un-

16. Lovering, J., and Craig, W. M.: Compound Comminuted Fracture of the Skull Complicated by Gas Bacillus Infection and Brain Abscess: Report of a Case, Proc. Staff Meet., Mayo Clin. **16**:660-663 (Oct. 15) 1941.

17. Otenasek, F. J., and Chambers, J. W.: Fulminating Gas Gangrene of the Brain: Report of a Case in a Civilian, J. Neurosurg. **2**:539-542 (Nov.) 1945.

18. Report by a Committee of Soviet Scientists: Gas Infections of the Brain as One Form of Serious Complication of Cerebro-Cranial Injuries, Brit. M. J. **1**:785-788 (June 26) 1943.

doubtedly made possible recovery from a great many abscesses of the brain due to the gas bacillus. These cases, however, have not reached the literature.

SUMMARY

A case of traumatic abscess of the brain due to the gas bacillus (Cl. perfringens) is reported.

The recovery of the patient is attributed to the surgical drainage of the abscess and to penicillin. Owing to an oversight, no antitoxin was administered, and the sulfonamide drugs were not used because of their toxic effect on the patient.

The specificity of penicillin in the treatment of infections due to the gas bacillus has been demonstrated by numerous cases reported in the past two years. Some of these are reviewed.

Six cases of abscess of the brain due to the gas bacillus have been found in the literature. In 4 of these 6 cases the patient recovered. The absence of systemic symptoms in most of these cases indicates that infections of the brain due to the gas bacillus remain localized and their prognosis is good if surgical drainage and chemotherapy are instituted as soon after the injury as possible.

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RELIEF OF SYMPTOMS FOLLOWING ENCEPHALOGRAPHY BY COMBINED PREMEDICATION AND USE OF OXYGEN

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THE INDICATIONS for pneumoencephalographic and pneumorachiographic studies are well known.[1] It is also well known that patients undergoing these procedures complain of severe headache for five days or more and are considerably incapacitated. It is not unusual to hear them referred to by patients in the ward as "skull busters," "nut crackers" and other terms signifying their great dread of and anxiety toward submitting to these diagnostic procedures. Many attempts to overcome such undesirable after-effects have been tried by various workers in the field.[2]

Liberson[3] described the use of various gases in an attempt to reduce the severe headache reactions to encephalographic procedures and concluded:

> . . . whereas the question of safety in encephalography has been dealt with and met in great part by the simultaneous displacement apparatus, nothing substantial has been found to obviate the discomforting post-injection headache. The displacement of the cerebrospinal fluid by gases other than air holds a little promise of less severe reactions, but headaches of moderate severity are still present in almost every case.[3a]

From the Division of Neurology and Psychiatry, United States Marine Hospitals, Stapleton (Staten Island), N. Y., and New York.

1. Rehwald, E.: Enzephalographie mit Luft, Med. Klin. **38**:1191 (Dec. 11); 1213 (Dec. 18) 1942. Mayfield, F. H., and Bell, J. C.: Pneumoencephalography in the Study of Sequelae of Head Injuries, South. M. J. **37**:142-149 (March) 1944. de Martel, T., and Guillaume, J.: L'encéphalographie gazuese par voie lombaire: Technique, résultats, indications, Monde méd., Paris **47**:793-802 (Aug. 1-15) 1937. Draper, P. A.: Therapeutic Pneumo-Encephalography, Dis. Nerv. System **3**:232-238 (Aug.) 1942. Dickerson, W. W.: Pneumo-Encephalography in Epilepsy, Am. J. Psychiat. **98**:102-109 (July) 1941.

2. von Storch, T. J. C., and Karr, H. H.: Reduction of Pain and Other Undesirable Reactions Due to Pneumoencephalography, New England J. Med. **224**:755-759 (May 1) 1941.

3. Liberson, F.: (*a*) The Use of Various Gases in Encephalography, Am. J. M. Sc. **185**:478 (April) 1933; (*b*) Apparatus for Simultaneous Displacement, Arch. Neurol. & Psychiat. **12**:300-304 (Sept.) 1924.

In 1937 Schwab, Fine and Mixter[4] described a technic for giving 95 per cent oxygen after encephalographic studies, using a specially built oxygen tent which administers oxygen at a rate of 10 to 14 liters per minute, and this apparatus was later replaced with a facial mask and gasometer for the administration of oxygen to the patient after the encephalographic study. This procedure required the attendance of a nurse for two to three minutes every thirty minutes to permit the expired air to escape into the atmosphere and carry off the nitrogen. The authors concluded that the inhalation of oxygen was followed by prompt removal of most of the subarachnoid air during the three hours the patient was

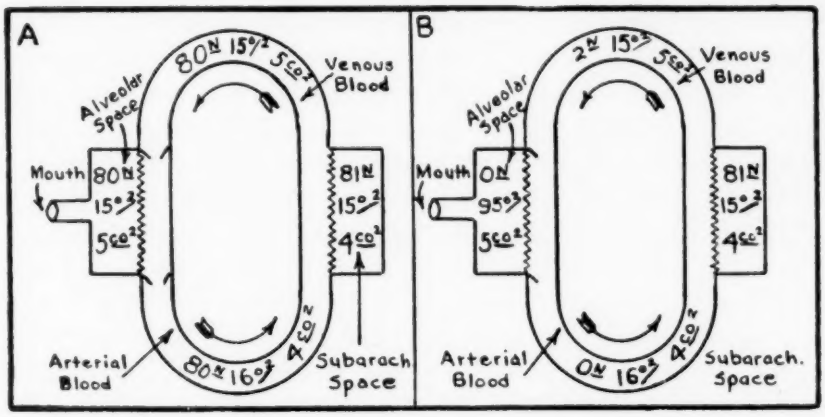

Fig. 1.—Diagrammatic scheme of the effect of 95 per cent oxygen on the absorption of air from the subarachnoid space; *A* shows the removal of subarachnoid air when air is breathed; *B*, the removal of subarachnoid air when 95 per cent oxygen is breathed. *N* indicates nitrogen; O^2, oxygen gas, and CO^2 carbon dioxide (Schwab, Fine and Mixter[4]).

in the machine. The reactions were reduced in most cases. The principle of oxygen therapy was adequately described in that paper and is briefly explained in their diagrammatic scheme, reproduced here (fig. 1).

PRESENT INVESTIGATION

The purpose of this paper is (1) to report the results of administration of 95 per cent oxygen after the encephalographic procedure by use of the ordinary hospital oxygen tent for a period of three or more hours in a series of 40 patients—merchant seamen, members of the Coast Guard and Coast Guard dependents—who were admitted to the neurologic service of the United States Marine Hospital, Stapleton, N. Y., and (2) to describe the preoperative preparation, which lessens the apprehension

4. Schwab, R. S.; Fine, J., and Mixter, W. J.: Reduction of Postencephalographic Symptoms by Inhalation of 95 Per Cent Oxygen, Arch. Neurol. & Psychiat. **37**:1271-1282 (June) 1937.

of the patient, reduces disturbing symptoms occurring during the procedure and affords excellent cooperation on the part of the patient before, during and after the encephalographic procedure.

The method here described was devised after the unfortunate reaction of an 11 year old boy on whom an encephalographic study was performed. He presented various types of choreiform movements and an abnormal behavior pattern following an attack of encephalitis at the age of 5 years. His encephalogram, unlike those in the other cases reported, was performed while he was under general anesthesia induced with intravenous injection of sodium pentothal. During the induction of the anesthesia, respiratory failure occurred for about twenty minutes, during which time resuscitatory measures were employed. After the return of normal respiration, the encephalographic study was completed, and the patient was returned to the ward and placed in an oxygen tent. The following morning (fifteen hours after the completion of the encephalographic study) the youngster was alert, sitting up and extremely anxious to get out of bed. He had no headache or other untoward effect.

Encephalographic studies on remaining patients in the series were performed in exactly the same manner, but with barbiturate premedication. Trial periods, during which the patient remained in the tent, varied from forty-eight hours, for the first 3 patients, to three hours, for the last 28. It was noted that as soon as the patient recovered from the premedication he was fairly comfortable and complained only of slight headache or a "swishing" feeling in the head when he turned his head from side to side. Roentgenograms were taken at intervals of three, nine, eighteen and forty-eight hours, in 12 cases, in an attempt to determine roentgenologically the amount of residual air in the ventricles and the subarachnoid space. It was finally determined that the use of the oxygen tent with 95 per cent oxygen for a period of three hours after the patient's return to the ward was most economical and efficacious in reducing postencephalographic symptoms, although the concentration of oxygen was less than that with the method reported by Schwab, Fink and Mixter. The use of the oxygen tent also aided in the rapid reaccumulation of cerebrospinal fluid in the subarachnoid and ventricular systems.

The second part of this study was carried on with a view to allaying the anxiety of the patient, obtaining the greatest cooperation during the performance of the procedure and reducing the amount of shock, characterized by moderate sweating, rapid changes in pulse rate and considerable retching and vomiting, without placing the patient under general anesthesia. Various types of premedication were tried; these consisted in use of pentobarbital, sodium amytal, vinbarbital sodium ("delvinal sodium") and an experimental barbiturate called E.P.424, put out by

the Winthrop Chemical Company, combined with administration of codeine, 1 grain (65 mg.) and scopolamine hydrobromide, 1/150 grain (0.4 mg.). The final medication arrived at was a combination of hexobarbital (sodium N-methylcyclohexenyl-methyl barbiturate; "evipal") and a preparation containing in each tablet 1 grain (0.065 Gm.) of hexobarbital and acetylsalicylic acid, 7½ grains, (0.56 Gm.) ("evicyl"). This combination was most effective in the reduction of symptoms of shock and vomiting and tended toward good cooperation on the part of the patient during the procedure and during the period required for taking the roentgenograms.

In most cases an attempt was made completely to empty the cerebrospinal fluid from the subarachnoid and ventricular spaces. The amounts varied from 120 to 210 cc. With patients under sedation with barbiturates other than hexobarbital and the aforementioned preparation of hexobarbital and acetylsalicylic acid, some difficulty was encountered

Clinical Data on Patients Receiving Premedication with Barbiturates Combined with Use of Oxygen After Encephalographic Study

Barbiturate	No. of Cases	Average Amount of Fluid Removed, Cc.	Average Amount of Air Replaced, Cc.	Severity of Symptoms During Procedure
Pentobarbital	3	133	122	Moderate
"Sodium amytal"	3	120	105	Moderate
Vinbarbital sodium	3	60	50	Severe
E. P. 424 (Winthrop)	3	72	61	Severe
Hexobarbital ("evipal") and preparation of hexobarbital and acetylsalicylic acid ("evicyl")	28	158	142	Mild

because of vomiting, sweating, poor pulse and decrease in blood pressure. With these patients, the procedure was terminated with removal of an average of 96cc. of fluid and injection of a corresponding smaller amount of air (table).

All the patients in this study were male, since male patients comprise the majority of persons admitted to hospitals under the existing regulations of eligibility for treatment by the United States Public Health Service. The youngest was 13 and the oldest 58 years of age. The age groups were distributed as follows:

Age Decade	No. of Cases
10—20	4
20—30	13
30—40	15
40—50	7
50—60	1

The classification according to the clinical diagnosis was as follows:

	No. of Cases
Epilepsy—petit and/or grand mal	10
Focal cortical seizures	2
Obliterative subarachnoiditis	2
Hydrocephalus external and/or internal, acquired	12
Traumatic encephalopathy	8
Post-traumatic headache	5
Acoustic neuroma, benign	1

In the first 12 cases following the initial case, roentgenograms taken at intervals after the encephalographic procedure showed that after the first three hours the amount of residual air in the subarachnoid space differed little from the amount remaining in cases in which the patient was left in the oxygen tent as long as forty-eight hours. Clinically, it was observed that all 28 patients who had been in the oxygen tent for three hours were as comfortable after that time as those who had been kept in the tent for longer periods, even up to two days.

No. of Cases	Period in Oxygen Tent, Hr.	Subarachnoid Air Present
3	48	Slight
2	18	Very slight
2	9	Moderate
5	3	Very slight

TECHNIC

No meal is allowed the patient for four to five hours preceding the encephalographic procedure. He is given an enema. Two hours preceding the beginning of the procedure he is given 2 tablets of hexobarbital ("evipal") (0.5 Gm.) by mouth, followed in one-half hour by 1 tablet (0.25 Gm.) of hexobarbital and 1 tablet (0.5 Gm.) of the preparation of hexobarbital and acetylsalicylic acid ("evicyl"). The latter dose is repeated during the next half-hour. One-half hour later he is given codeine, 1 grain, and scopolamine hydrombromide, 1/150 grain, hypodermically.

The patient is then placed on a Trendelenburg stretcher and taken to the x-ray room. He is placed on a chair of the type used by roentgenologists in performing fluoroscopic examinations. This chair is placed on a small platform equipped with four casters, so that, after withdrawal of the cerebrospinal fluid and injection of air, the patient may be moved to the x-ray machine without disturbing him. In this sitting position, with the patient's back facing the operator and his chin resting on a concavity on the back of the chair, the skin is aseptically prepared. A lumbar tap between the third and the fourth vertebra is done in the usual manner with a 20 gage spinal needle. We have used a simple set-up, consisting of a 10 cc. syringe and a rubber tubing containing an adapter for the needle and for the tip of the syringe. A three way stopcock may be utilized between the syringe and the rubber tubing to facilitate emptying of the spinal fluid and the injection of room air. Initially, 10 cc. of fluid is removed and replaced with 5 cc. of room air. This is followed by removal of 5 to 10 cc. of fluid and replacement with 5 to 10 cc. of room air. The procedure is allowed "to do itself," without any attempt to hurry it along by drawing on the barrel of the syringe.

The simple syringe and needle method was chosen in preference to the automatic, continuous flow technic devised by Liberson in 1924 or that of von Storch,[5]

5. von Storch, T. J. C.: On Technique of Encephalography with Special Reference to Use of Apparatus, Am. J. Roentgenol. **35**:78-92 (Jan.) 1936.

described in 1935. Our procedure allows for the withdrawal of as much or as little fluid, and the replacement of as much or as little air, as is considered advisable by the operator at any particular time consistent with the condition of the patient. This is continued until the subarachnoid and ventricular systems are partially or completely emptied. Samples of spinal fluid are collected for laboratory study.

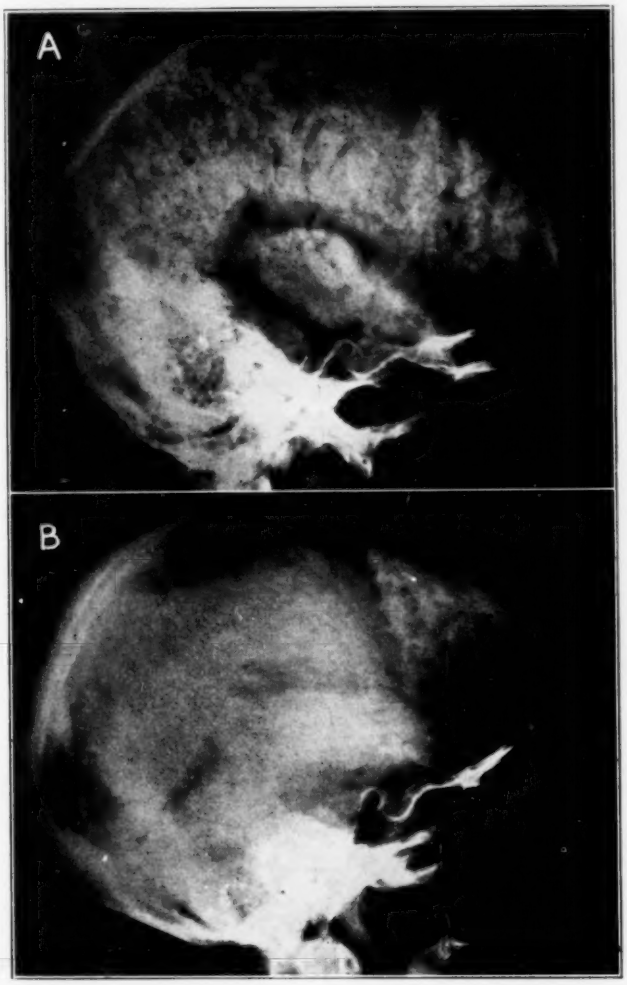

Fig. 2.—*A*, lateral encephalogram in a case of benign acoustic neuroma, taken immediately after the injection of 180 cc. of air. *B*, roentgenogram in the same case as that illustrated in *A*, taken after the patient had been eighteen and a half hours in an ordinary oxygen tent, with 95 per cent oxygen administered at the rate of 8 liters per minute.

After the encephalographic procedure, the patient is returned from the x-ray room on the Trendelenburg stretcher in the Trendelenburg position to his bed, which has been prepared as an ether bed. He is immediately placed under an ordinary hospital oxygen tent. Ninety-five per cent oxygen is administered at a rate of 8 liters per minute for a period of three hours. The foot of the bed is

elevated on shock blocks for twenty-four hours; the blocks are then removed. Fluids are forced on the night of the operation, followed by a soft, and then a regular diet.

OBSERVATIONS

The combined use of the barbiturates hexobarbital and the preparation of hexobarbital and acetylsalicylic acid permits a smoother and

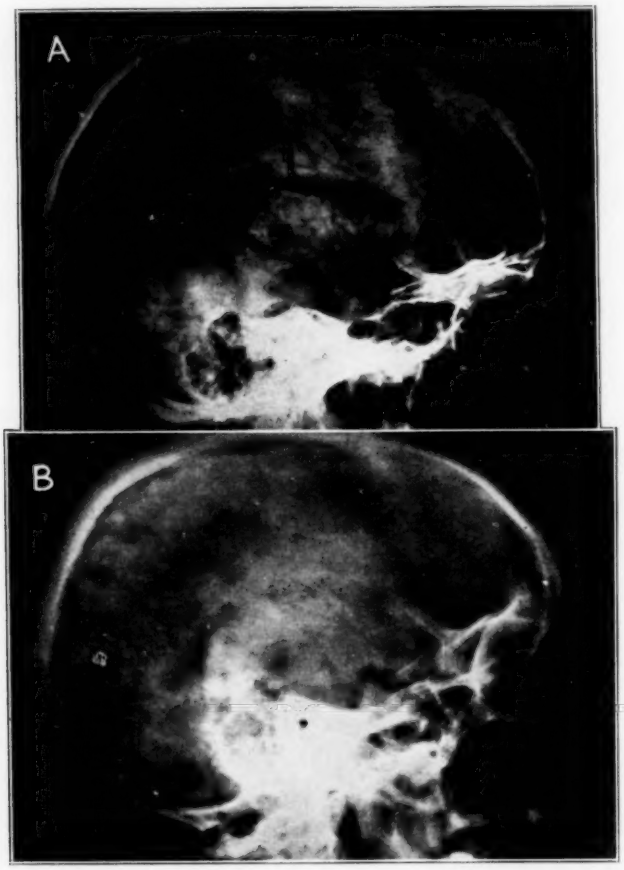

Fig. 3.—*A*, lateral encephalogram in a case of grand mal epilepsy in a 44 year old member of the Coast Guard, taken immediately after the introduction of 195 cc. of air.

B, roentgenogram in the same case as that illustrated in *A*, taken after the patient had been two and a half hours in an ordinary hospital oxygen tent, with 95 per cent oxygen administered at a rate of 8 liters per minute.

easier technical procedure, with better cooperation of the patient, fewer symptoms of shock, either mild or severe, than does the use of other barbiturates, with which there are considerable difficulty in carrying out the examination and more symptoms and apprehension on the part of the patient. The pulse rate varies slightly, within a range of 5 to 10 beats

per minute, during the entire procedure. Perspiration is negligible, or is not present in some cases. Retching and vomiting occur with less frequency than with other barbiturate preparations.

When the patient has completely recovered from the medication and has been in the oxygen tent for three hours, he is comfortable and has few complaints except on movement of his head, and then complains only of slight headache. When the patient has been placed in bed under the tent, special nursing care is not required at periodic intervals. Occasionally vomiting occurs while the patient is under the tent. All symptoms disappear in an average of two or two and one-half days. The availability of the ordinary oxygen tent in all hospitals and the simplicity of the apparatus used reduce the cost of operation and make unnecessary any special equipment.

SUMMARY

The results are reported in 40 cases in which 95 per cent oxygen was administered at a rate of 8 liters per minute by means of the ordinary hospital oxygen tent after the encephalographic procedure. This treatment resulted in the reduction of the severe symptoms which usually follow this procedure. The symptoms present were minimal, and the patient was comfortable immediately after recovering from the preliminary sedation.

In 28 of these cases excellent results were obtained after the patient had been in the oxygen tent for three hours.

The use of the oxygen tent aids in the reaccumulation of the cerebrospinal fluid. Its ready availability in all hospitals reduces the unnecessary expense of special equipment and special nursing care and attention.

Various types of barbiturate premedication were used to allay the anxiety of the patient and to secure his cooperation before, during and after the encephalographic procedure. The combination of hexobarbital ("evipal") and a combination of hexobarbital and acetylsalicylic acid ("evicyl") was superior to other barbiturates in this respect.

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ORIGIN OF THE THEORY OF CONDITIONED REFLEXES

Sechenov; Hughlings Jackson; Pavlov

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THE TERM "conditioned reflex" was introduced by Pavlov in 1903. He mentioned it for the first time in an oration entitled "Experimental Psychology and Psychopathology in Animals," which he delivered at the International Congress of Medicine in Madrid in April of that year.[1]

By a conditioned reflex Pavlov meant a response, established in an animal, to one or more unessential properties of a stimulating object. These properties, the sight or smell of food, for example, act through the appropriate receptive surface—the eye or the nose in this case—while the main receptive surface which is of concern here (the mucous membrane of the mouth cavity) remains unaffected. The conditioned response requires the participation of the central nervous system, especially that of the cerebral cortex, which may be considered the chief organ of conditioned reflexes. After the removal of the cerebral cortex in animals, only crude conditioned reflexes can be established, for which certain, as yet unknown, subcortical parts are responsible.

The conditioned response is a typical of reflex: An afferent impulse, which originates on the surface of the body, or within it, is conveyed to a center or centers in the central nervous system and thence is transmitted through the efferent channels to a peripheral organ—a gland or a muscle. A conditioned reflex is based on an unconditioned reflex, which is the inborn reaction of an animal to the essential properties of some external or internal stimulus. The arc of this reflex passes through the spinal cord or the lower parts of the brain. An unconditioned reflex will

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This paper, which was read at the meeting of the Montreal Neurological Society, March 19, 1947, is based in part on material contained in a biography of I. P. Pavlov prepared by the author and to be published by the University of Chicago Press. The work of Sechenov and Pavlov was discussed by the author in more popular form in the *Russian Review* (Spring Issue, 1946, p. 24).

1. Pavlov, I. P.: Lectures on Conditional Reflexes, New York, International Publishers, 1928.

persist after surgical removal of the cerebral cortex or the elimination of its functions by anesthetics.

It was long believed, and is still believed by many, that almost all the movements of a highly organized animal, such as the dog, when it is in a conscious state, are controlled by its mind. Again, when it was discovered that a dog salivates or secretes gastric juice merely on seeing or smelling food, this response was regarded as a psychic phenomenon and was called a "psychic secretion" of saliva or of gastric juice.

How is one to reconcile these two concepts—the mechanistic and the psychologic, the reflex action and the free expression of will in an animal or in man? Although it is probable that consciousness is only partly dependent on the cerebral cortex, which is the chief organ of the conditioned reflex, nevertheless, this part of the brain contributes immensely to the pyschic life of animals and man. A dog from which the cerebral cortex has been removed surgically is a complete invalid, although undeniably consciousness may still be present. From the psychologic point of view such a dog is mentally deficient; it is an idiot, and is unable to find food that is put before it or to recognize its master; it sleeps most of the time and awakes only when it is hungry or requires to empty its pelvic reservoirs. True, no conditioned reflexes, save a very few imperfect ones, can be formed in a decorticated dog. But is this due to the destruction of the nervous system's machinery for the formation of conditioned reflexes or to defects in the animal's mentality and a complete distortion of its psychic life?

Pavlov definitely and repeatedly stated that all psychic manifestations of animals such as the dog are based on conditioned reflex action. The reflex is always initiated by a stimulus—an impulse reaching the central nervous system from the periphery; it never originates spontaneously in the brain. The behavior of an animal may or may not be reflected in consciousness, but consciousness is not the initiator of the conditioned reflex. From this it follows that in order to establish and sustain the proper relationship of the organism with the surrounding environment the animal's conditioned reflex mechanism must be in perfect order.

A question that will arise in the minds of many people is: What right had Pavlov to consider as a reflex one of the most complicated functions of the body, which is connected in some way with the consciousness of an animal? Or, to put this question in another way: Is a conditioned reflex a reflex, or is this particular reaction a psychic phenomenon, which depends on the animal's will or desire and only simulates a reflex action?

One touches here on one of the fundamental problems of the physiology of the nervous system. The function of the whole central nervous system, with the exception of the cerebral hemispheres, was conceived mainly as based on reflex action. Only the cerebral hemispheres were ex-

cluded from this purely physiologic approach. The investigator was unable to explain their function from a physiologic point of view because it was so closely bound up with the animal's consciousness. He was forced to address himself to another discipline—psychology. Thanks to the work of Pavlov and his school, one is now in the fortunate position of being able to apply physiologic methods to the study of the cerebral cortex. The law of reflex action, already firmly established for all other parts of the central nervous system, can now be legitimately applied to the cerebral cortex. This does not in any way diminish the value of psychologic study of animal, especially human, behavior. The coalescence of physiology and psychology is perhaps not so far off as it seems.

Great as is the contribution of Pavlov in the extension of physiologic thought and methods to study of the higher manifestations of the activity of the central nervous system, he was not the first to follow this path. The theory of conditioned reflexes did not spring from his brain like a *deus ex machina.* He had predecessors, perhaps no less great than himself. One of these was another Russian, Ivan Michailovich Sechenov (1829-1905), the father of Russian physiology. Another was Hughlings Jackson (1834-1911), an eminent English neurologist and a great thinker. Sechenov regarded the function of the cerebral cortex as based on reflex action. He spoke of the "reflexes of the brain." Jackson repeatedly emphasized the sensorimotor arrangement of both the lower and the higher centers in the brain. The activity of the latter was only "concomitant" with the activity of consciousness. A great experimenter, Pavlov adapted these theoretic conceptions to experimental study to aid him in formulating his own theory of the cerebral functions, and thus opened up an unlimited field of investigation.

It will now be shown how Sechenov and Jackson made Pavlov's teaching of conditioned reflexes possible.

SECHENOV

In 1863 Sechenov made a daring attempt to explain the phenomena of psychic life from a physiologic point of view. As he wrote: "All the endless diversity of the external manifestations of the activity of the brain can be finally regarded as one phenomenon—that of muscular movement" (Sechenov,[2] 1935, p. 264). It was Sechenov's main theory that not only all involuntary, but all voluntary movement is based on reflex action. He stated:

> [Voluntary activity] is composed of reflexes which begin with sensory excitation, continue by means of a definite psychic act, and end in muscular movement . . . The final member of every voluntary act, i.e., muscular movement, is

2. Sechenov, I.: Selected Works, Moscow, State Publishing House, 1935.

identical with the action of muscles in pure reflexes, i.e., in elementary involuntary movements [page 291].[2]

The machine-like character of involuntary movement is not disputed by any one. But, according to Sechenov, the same character must be ascribed to voluntary movement, in spite of its seeming independence of sensory stimulation.

It is difficult to perceive clearly the reflex nature of a voluntary act performed by an adult person, but the formation of various associations in a child from birth affords good evidence that the voluntary movements originate as reflexes.

Sechenov illustrated this by the following example: For the first time in his life a child touches a bell. The muscular and tactile sensations are accompanied in this case with a visual impression and an acoustic sensation. If the touching and the ringing of the bell are repeated several times, a complex optic-acoustic-kinesthetic-tactile association is formed. The sensory stimulations originate a conscious process in the child's brain. At this stage not only the coolness of the metal and the weight of the bell, but the sight of the bell and the sound which it produces denote a definite object. Sechenov[2] continued (page 297):

Now see what this leads to; the consecutive series of reflexes gives a very complete idea of the object, it imparts knowledge in its elementary form.

The analytic functions of the brain are also based on reflex action. Here is the disintegration of a concrete impression into its elements. For example, let it be imagined that a person is standing in front of an infant. Through his retina the infant receives a summary impression of the person before him, say his mother. By moving his eyes, with the aid of the ocular muscles, he is able to distinguish the different parts of his mother's body. This is not necessarily an act of volition, since an infant would involuntarily follow with his eyes the movements of the arms, head and other members of a person standing before him. In this way a visual impression is coupled with a purely reflex muscular act.

A reflex action, when repeated several times, leaves a definite trace in the central nervous system. This after-effect of stimulation is preserved in latent form in the cells of the brain and may be revived later. This is what is called memory. It is not the case that one remembers things merely by an effort of will. Sechenov expressed the belief that the recurrence of past events in consciousness is also due to a reflex. He asserted that the most complex associations are nothing more than "an uninterrupted series of contacts between the end of each successive reflex with the beginning of the next one [page 312]."[2] The slightest, scarcely noticeable, hint at any point in the association results in the reproduction of the entire association. Sechenov[2] gave the following observation in support of his theory (page 316):

I devote my day to physiology, but at night while going to bed it is my habit to think of politics. It happens quite naturally that among other political matters I sometimes think of the Emperor of China. This acoustic trace [Sechenov means the sound of the words "emperor of china"] becomes associated with the various sensations (muscular, tactile, thermic, and so on) which I experience when lying in bed. It happens occasionally that, owing to fatigue or having no work to do, I lie down on my bed in the day-time, when lo! all of a sudden I notice that I am thinking of the Emperor of China.

A reflex beginning with a sensory stimulation does not invariably end in a muscular contraction. According to Sechenov, reflexes occur where the end is inhibited and no movement results. The property of inhibiting a movement belongs to the central nervous system, and not to the antagonistic muscle.

In 1862, not long before Sechenov wrote his book on reflexes of the brain,[3] he made the startling discovery that stimulation of the optic thalami of a frog by placing a crystal of common salt on them inhibited the movement of the hindlegs which is their usual reaction on being dipped in a weak solution of acid (Türck's method). He stated the belief that he had found a center for inhibition of coordinated muscular movements (Sechenov,[2] page 153).

It was only natural that Sechenov should generalize from the results of his experiments and attempt by their means to explain certain psychic phenomena. He expressed the belief, for instance, that man owes his capacity to think, deliberate and judge to reflexes with an inhibited end. "A thought," he wrote, "is the first two thirds of a psychic reflex [page 321]."[2] On the other hand, the emotions, which are also of a reflex nature, being induced by an external stimulus, are psychic reflexes with an unproportionally augmented end.

In summarizing his argument, Sechenov stated that the initiation of all forms of human activity depends on the impressions which the organs of sense receive from without or from within the body. If no impulses reach the central nervous system from the organs of sense, the psychic life will be annihilated. He made the remarkable assertion that "a man in a dead sleep and without sensory nerves would sleep to his death [page 336]."[2]

Indeed, about thirteen years after the appearance of Sechenov's "Reflexes of the Brain,[3] Strümpell[4] described the case of a 16 year old boy deprived of almost all his organs of sense. (Two other such cases were reported, by Heyne[5] and by von Ziemssen,[6] both in 1891.) Strümpell's

3. Sechenov, I.: Physiologische Studien über die Hemmungsmechanismen für die Reflexthätigkeit des Rückenmarks im Gehrins des Frosches, Berlin, A. Hirschwald, 1863.

4. Strümpell, A.: Arch. f. d. ges. Physiol. **15**:573, 1877.

5. Heyne, M.: Deutsches Arch. f. klin. Med. **47**:75, 1891.

6. von Ziemssen, H.: Deutsches Arch. f. klin. Med. **47**:89, 1891.

patient had no sense of taste or smell and was deaf in his right ear and blind in his left eye; his skin, mucous membranes and muscles were devoid of sensibility. When the boy's normal eye was closed and his normal ear plugged, he fell into a deep sleep in two or three minutes. Waking could be effected only by light acting on his normal eye or sound on his normal ear. Shaking him did not arouse him.

Sechenov regarded his conception of the psychic life of man as a hypothesis only and formulated it as follows:

> Under similar external and internal conditions men must act in the same way. The choice of one out of many possible ends of the same psychic reflex is definitely impossible, and its apparent possibility is only an illusion of our consciousness . . . The real cause of every human activity lies outside man [pages 333-334].[2]

J. HUGHLINGS JACKSON

Jackson's conception of the function of the brain and of the relation of its physiologic to its psychologic processes is close to the ideas of Sechenov on the subject, although in all probability Jackson never read the "Reflexes of the Brain." (There was, however, a contemporary French translation of Sechenov's treatise.)

According to Jackson,[7] there is a sensorimotor arrangement, consisting of sensory and motor centers, throughout the whole central nervous system. However, from the functional point of view the connections between these centers differ at various levels of the central nervous system. Jackson stated the belief that there are three levels of "evolution" in the central nervous system. ("Evolution" is the term of the philosopher Herbert Spencer. It denotes, in the case of the nervous system, the passage from the most organized, simplest and most automatic to the least organized, most complex and most voluntary—in other words, a gradual transition from the lowest to the highest centers.)

The hierarchy of the nervous centers, according to Jackson, is as follows: 1. The lowest level extends from the tuber cinereum to the conus medullaris. 2. The middle level is represented by the rolandic region of the cerebral cortex with its motor centers, and also possibly the ganglia of the corpus striatum. 3. The highest level includes the centers of the prefrontal and occipital lobes. The mechanism that sets the sensorimotor centers in action at all three levels is the same throughout—it is the mechanism of reflex action.

The sensorimotor centers at the lowest level represent the whole body from "nose to feet"; they are the simplest, but most organized. They are representative centers.

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7. Jackson, J. H.: Selected Writings, edited by J. Taylor, London, Hodder & Stoughton, (*a*) 1931, vol. 1; (*b*) 1932, vol. 2.

The sensorimotor centers at the middle level are more complex and less organized than the centers at the lowest level. They indirectly represent wider regions than the latter. Since the same regions are already represented in simpler form by the centers of the lowest level, those at the middle level are re-representative.

At the highest level of the nervous system are the highest motor and sensory centers. These centers are the most complex and least organized; they indirectly represent the widest regions of the body. They are re-representative. Jackson stated the belief that the highest centers are "the organ of mind" or "the anatomical substrata of consciousness." As he wrote[7a] (pages 349 and 414), "they are sensory-motor as certainly as the lumbar enlargement is."

This brings one to a point in Jackson's teachings which is of particular interest here and now. What relation do the centers of the highest level bear to consciousness or to the mental state in general? Jackson rejected the materialistic hypothesis and advanced his own doctrine of concomitance. According to this doctrine, the "state of consciousness" is quite distinct from the "nervous state," but the two states always occur together, though the one does not interfere with the other. Jackson vehemently denied that special centers for volition, ideation, reasoning and emotions exist in the brain (Croonian lecture,[7b] page 45). He stated the belief that the activity of the highest, least organized, sensorimotor arrangement is determined by the activity of the lower, more organized, arrangements. This statement by Jackson may be taken to mean that the response of the highest centers and the concomitant conscious state depend on reflex action.

According to Jackson[7a] (page 240), one's "ideas" are acquired by experience "during the correspondence betwixt the organism and its environment. . . The sensory-motor arrangement we have been speaking of constitutes the inherited mechanism by which these correspondences can be affected."

Whereas Sechenov's conception of the reflexes of the brain was purely theoretic, Jackson's teaching was based to a great extent on clinical material. Many of Jackson's statements are valid today, though some of his hypotheses have not been confirmed. One of the latter was the role of the prefrontal lobes. Jackson expressed the belief that they contained the highest motor centers for all parts of the body, a claim which was disputed even in his own time by Ferrier (Jackson,[7b] page 63). Again, Jackson asserted that the "highest centers," which he thought to be situated in the prefrontal region of the cerebral cortex, are, as already stated, "the organ of mind," or "the anatomical substrata of consciousness." It is now known that such functions cannot be ascribed to this part of the brain (Penfield,[8] 1938; LeBeau,[9] 1942).

Like Sechenov, Jackson believed that a muscular movement is an obligatory component of every psychic act, initiated by a stimulus acting on one of the receptive surfaces of the body. How closely the conceptions of Sechenov and Jackson approached each other is shown by the following observations: Sechenov[2] (page 312) pointed out that in early childhood the acoustic sensations are closely associated with muscular sensations which arise in the chest, the throat and, especially, the tongue and the lips. Thus speech arises, and speech is closely related to thinking. Small children cannot think without speaking, and most adults think in words, or in those muscular sensations which accompany a thought when it is spoken.

"I urged for years," wrote Jackson[7a] (page 50), "that the anatomical substrata of words are motor processes." According to Jackson, there are two kinds of speech, an external and an internal; "there are discharges of the highest sensory-motor processes when we think, just as there are of the lower processes when we walk."[7a]

It is interesting to note that Laura Bridgman, who was deaf, dumb and blind, and who learned the finger language of the deaf-mute, expressed her thoughts, even in her dreams, by using this language with great rapidity (Watson[10]).

PAVLOV

Sechenov's and Jackson's conception of the activity of the brain, or, more correctly speaking, of the cerebral cortex, were the highest points attained by physiologic thought in the last third of the nineteenth century. It must not be forgotten that in this period psychology was purely introspective. Even the establishment of experimental psychology by Wundt in the seventies did not substantially change the general trend of this science. But psychology and physiology were moving toward a unification of the two. In psychology, dualism, which recognized the mind or soul and the body as two different entities, was gradually being replaced by monism, signifying the identity of mind and body relations. Physiology, on its part, was persistently propagating the conception of reflex action from the spinal cord and lower parts of the brain to the subcortical ganglia, still not daring to apply it to the cerebral cortex.

One of Pavlov's great achievements was that he considered the activity of the cerebral cortex from a purely physiologic point of view. He maintained that this activity was based on reflex action, just as was the activity of the rest of the central nervous system, although the reflexes

8. Penfield, W.: The Cerebral Cortex in Man, Arch. Neurol. & Psychiat. **40**:417 (Sept.) 1938.

9. LeBeau, J.: Rev. canad. de biol. **1**:134, 1942.

10. Watson, J. B.: Behaviorism, New York, W. W. Norton & Company, Inc., 1925, p. 241.

of the cerebral cortex were somewhat different from ordinary reflexes. With the aid of his method of conditioned reflexes, Pavlov studied the physiology of the cerebral cortex. The theory of conditioned reflexes was a direct continuation of, and a logical sequel to, the work of Sechenov and Jackson.

But Pavlov made another step forward. In his investigations he studied the physiologic functions of the cerebral cortex quite separately from its supposed psychic activity, something that had never been done before. Every reaction of the normal animal which had previously been considered a psychic act he treated as a cortical reflex. Thus, Pavlov studied the physiology of the cerebral cortex, and nothing else. But this physiologic study naturally included what had hitherto been called the psychic life of the animal. This was a daring innovation, because it established the undisputed right of the physiologist to apply his own methods in studying the functions of those parts of the brain which had always been regarded as the "organ of the mind," and were the special province of psychologic investigation.

In order to avoid a possible misunderstanding, it should be emphasized that Pavlov's teaching is pure physiology of the cerebral cortex. It is not concerned with the essence of consciousness or with mind. Pavlov, of course, never discussed the consciousness of his experimental animals. But, as to the place occupied by the concept of consciousness in the teaching of conditioned reflexes, it would be correct to say that this teaching deals only with the mechanism by which the consciousness is brought into contact with the outer world or with the internal organs of the animal. Pavlov never wished to deny psychology the status of a science or in any way to depreciate the highest aspirations of the human mind. In his own words[1] (page 129):

> . . . I do not deny the right of psychology to be regarded as a body of knowledge concerning the internal world of man. Even less am I inclined to negate anything that relates to the innermost and deepest strivings of the human spirit.

Like Sechenov, Pavlov regarded the higher manifestations of the cerebral activity as reflex in nature. Three fundamental principles on which the reflex activity of the cerebral cortex is based were formulated by Pavlov,[11] as follows (page 125): (1) the principle of determinism, i.e., "an impulse, appropriate conditions, or a cause for any given action or effect"; (2) the principle of analysis and synthesis, i. e., "the initial decomposition of the whole into its parts or units, and the gradual reconstruction of the whole from these units or elements"; (3) the principle of structure, i. e., "the distribution of the activity of force in space, the adaptation of function to structure."

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11. Pavlov, I. P.: Conditioned Reflexes and Psychiatry, New York, International Publishers, 1941.

As previously mentioned, Pavlov was convinced that a "conditioned reflex" is indeed a reflex. All the evidence supports this view. A conditioned reflex is always initiated by a stimulus which acts on one of the receptive surfaces of the body and is not generated spontaneously in the consciousness of the animal. Although the activity of the cerebral cortex is linked in some manner with the conscious state, this in no way alters the reflex nature of the conditioned response.

Several facts support the view that the conditioned reaction is a true reflex.

1. Although for the formation of a conditioned reflex in an animal a state of alertness is necessary, a reflex may be formed even when the consciousness is not, or cannot be, focused on the stimulus which evokes this reflex. This is what occurs when an infant is learning to walk or talk, or when one encounters a new person, place or phenomenon that seems to be strangely familiar, for one has indeed seen it all before, although it has not been reflected in consciousness. Nevertheless, consciousness often does participate in the formation of conditioned reflexes.

2. A firmly established conditioned reflex, as everybody knows, may be reproduced quite unconsciously, like an unconditioned reflex. This is an extremely important point, since it shows that a conscious reaction follows the same neural paths as an unconscious one.

3. Again, a purely unconditioned reflex, such as the knee jerk, may be reflected in one's consciousness.

4. A number of reflexes, like deglutition or emptying of the pelvic reservoirs, which are performed unconsciously by an infant, gradually become conscious acts.

5. The problem of voluntary movement presents more difficulty. Pavlov explained its reflex nature by means of the following example (Pavlov[12]): A dog is told to give its paw; the paw is lifted by its master, and the animal then receives a piece of food as a reward. During this act three cortical areas are simulated; the auditory area, the kinesthetic area (passive movement of the paw) and the gustatory area, which is closely associated with the food center. After several repetitions of this procedure, the words of command produce the desired effect; that is, the auditory stimulation is transmitted to the corresponding motor cells. But when the animal is hungry, it lifts its paw without the words of command, and so produces a voluntary movement. Pavlov interpreted this as showing that in the cerebral cortex the neural process may move in opposite directions: either from the kinesthetic cells to the auditory and gustatory cells, as in the formation of a conditioned reflex, or from the

12. Pavlov, I. P.: Tr. Pavlov's Physiol. Lab. **6**:115, 1936.

gustatory cells and the food center to the kinesthetic cells, as in a voluntary movement. Pavlov himself admitted that this interpretation left unsolved the problem of the connection between the kinesthetic and the motor cells of the cortex. He was inclined to think that this connection is not inborn, but acquired.

In view of all these considerations, there seems to be little doubt that in the dog the response to a conditioned stimulus is a reflex, though this reflex has certain peculiarities which make it different from an ordinary, unconditioned reflex.

It is a remarkable fact that the difference in the respective reflex mechanisms of the lower and higher parts of the central nervous system had already been clearly conceived by Jackson in 1875[7a] (page 60). He expressed the same idea even more forcibly twenty-three years later, in 1898[7b] (page 437):

> If the "vital" centers of the lowest level were not strongly organized at birth, life would not be possible; if the centers of the highest level ("mental centers") were not little organized and therefore very modifiable, we could only with difficulty adjust ourselves to new circumstances and should make few new acquirements.

This statement is virtually a recognition of the two types of machinery existing in the central nervous system: one is the spinal cord and in the greater part of the brain, for unconditioned reflexes; the other in the cerebral cortex, for conditioned reflexes. At the end of the nineteenth century, however, the time was not yet ripe even for such a great man as Jackson to reject the psychologic interpretation of the functions of the cerebral cortex and consider them from a purely physiologic point of view. To develop a new idea, a new man was needed, and that man was Pavlov.

The Cerebral Cortex and the "Center of Consciousness."—As has already been noted, Pavlov completely excluded the problem of consciousness from his studies of the physiologic function of the cerebral cortex. How wise a step this was has been shown by the remarkable work done by Penfield[8] and confirmed by LeBeau.[9]

These investigators established that in patients subjected to operations on the brain the cerebral cortex is not essential to the conscious processes. Consciousness depends on the integrity of the region comprising the anterior and inferior parts of the lateral walls of the third ventricle. As a result of damage or removal of this area of the brain alone—for brevity's sake, I shall call it temporarily the "center of consciousness"—a person becomes unconscious.

This startling discovery throws a new light on the functions of the cerebral cortex. It lends support to Pavlov's conviction that the cerebral

cortex consists of the central ends of the analyzers, by which he meant the organs of sense or the other receptive surfaces of the body with nerves and centers in the central nervous system.

It seems to me that on the evidence of all the known facts one may make an attempt to interpret the relation between the cerebral cortex and the "center of consciousness." In this discussion I shall approach "consciousness" from a purely factual point of view, ignoring any psychologic or metaphysical considerations. To a physiologist or to a medical man consciousness is a reality which he must take into account in dealing with an animal or a human being.

What is the relation between the cerebral cortex and the "center of consciousness"? If consciousness is lost, the conditioned reflexes disappear and new ones cannot be formed, although most of the unconditioned reflexes are retained. This happens, for instance, under fairly light anesthesia or in decerebrate animals. Therefore the active state of the region in the anterior part of the third ventricle is essential for the normal conditioning function of the cerebral cortex. However, as was said before, although the "center of consciousness" must be in an alert state for the formation of a conditioned reflex, the direction of consciousness toward the conditioned stimulus is not absolutely necessary.

Thus, a close relationship exists between the cerebral cortex and the adjacent subcortical region containing the "center of consciousness." This is understandable, since in the lower vertebrates, such as the fishes, the rostral end of the telencephalon was never transformed into a cerebral cortex. In these species one finds only the olfactory lobes and a primitive forebrain, consisting of the thalamus and the corpus striatum. In teleosts the roof of the telencephalon, or pallium, is thin and nonnervous. Yet it was possible to form various conditioned reflexes in these fishes (Froloff[13]).

If the "center of consciousness" is necessary for maintaining normal activity of the cerebral cortex, many facts indicate that the proper functioning of the latter is essential for an adequate response of the "center of consciousness" to a conditioned stimulus. One might say that the "center of consciousness" is dead if the cerebral cortex does not function. A few examples may be given to illustrate this.

It is an indisputable fact that proper relations between the body and the surrounding medium are established through the cerebral cortex by means of conditioned reflexes. A decorticated dog which has lost practically all its conditioned reflexes and is unable to form new ones retains its consciousness, but this consciousness has almost no value for the animal.

13. Froloff, J.: Arch. f. d. ges. Physiol. **208**:261, 1926; **220**:339, 1928.

If one of the cortical analyzers, say the auditory, is partially damaged in a dog, a phenomenon occurs which Munk[14] called "psychic deafness" (or "psychic blindness" in the case of damage of the visual analyzer). He interpreted this from the psychologic point of view, stating that "the animal hears (or sees) but fails to understand." Physiologic study of this phenomenon by means of conditioned reflexes (Babkin, 1910, 1911; Pavlov,[15] page 335) showed that the function of the cortical auditory area was greatly impaired. The dog was still able to make the cruder differentiations required in distinguishing between three tones (the animal distinguished 120 vibrations from 135 or 165 vibrations per second) but lost for good the capacity to distinguish between a sequence of four ascending tones and the same sequence of four tones descending. Undoubtedly, both in the case of the single tones and in that of the sequence of tones the dog heard the sounds, since this was evident from its behavior. But in the former case the remaining parts of the damaged acoustic analyzer were sufficient to enable the animal to distinguish between the positive and the negative conditioned tones. The impulses were correctly transmitted to the "center of consciousness." In the latter case the ability to make the finer differentiation between a sequence of ascending tones and a similar sequence of descending tones was lost, owing to the destruction of the cortical machinery subserving this type of fine discrimination. From these facts, one may draw the conclusion that if a cortical analyzer does not function properly it is unable to transmit more complex impulses to the center of consciousness in a regular manner. Thus, the center of consciousness becomes useless.

Recently I learned about most interesting experiments made on the chimpanzee by Dr. A. H. Riesen,[16] of the Yerkes Laboratory of Primate Biology in Orange Park, Fla. (Dr. Riesen sent me the manuscript of his paper, which had not yet been published, and permitted me to cite his data.)

Two chimpanzees were reared in total darkness from the day of birth. Before the tests of their visual function were started, 1 of them had spent sixteen months, and the other fourteen and one-half months, in darkness. For feeding purposes, throughout these periods the first monkey was subjected to forty hours, and the second to thirty-four hours, of light in all.

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14. Munk, H.: Ueber die Functionen der Grosshirnrinde, Berlin, A. Hirschwald, 1890.

15. Pavlov, I. P.: Conditioned Reflexes, London, Oxford University Press, 1927.

16. Riesen, A. H.: First Visual Function of Chimpanzees Reared in Darkness, to be published.

Study of the effect of light on these chimpanzees after such a prolonged, and practically continuous, sojourn in total darkness gave the following results: Sudden subjection to light (produced by the turning on of a 40 watt lamp in darkness) evoked a prompt pupillary response. Orientation to light was pronounced. The optokinetic response to light (a flashlight in a dark room) was manifested by the animal's compulsive following of the light with its eyes. The optokinetic nystagmus to a rotating striate cylinder (known as railroad nystagmus) was evident in 1 infant monkey from the first test, and in the other from the second test.

In spite of their evincing good retinal sensitivity to light, the animals did not produce a protective squint or lid closure in response to a strong illumination, or when an object was brought close to their eyes. This reaction developed later, with more experience.

Visual fixation of objects, faces, color or moving figures was not obtained in spite of repeated attempts. The sight of objects with which the animals were familiar tactually or kinesthetically evoked no response at all. Thus, the sight of a feeding bottle did not evoke any reaction in the hungry infant chimpanzee. But if the nipple came in contact with any part of the monkey's face, or if the animal chanced to touch it with its hand, it quickly conveyed the bottle and nipple to its mouth. Thus, accurate tactual localization was developed in the animals.

Speaking psychologically, it is clear from these experiments that the chimpanzee did not possess any "visual consciousness" whatever, whereas other varieties of consciousness, such as the tactile, kinesthetic and auditory senses, were perfectly developed.

Dr. Riesen's experiments are of a preliminary character, and his investigation is not yet complete. Nevertheless, the importance of these findings is evident. The question may be asked: To what is the absence of the visual response due—to the inability of the cortical visual area to respond to the appropriate stimuli, because of the complete lack of visual conditioned reflexes, or to the prolonged inactivity of the corresponding parts of the "center of consciousness"?

The aforementioned facts concerning the normal sensitivity of the retina to light in monkeys reared in darkness and the observations and experiments dealing with the acquisition of visual control by these animals incline one to the belief that the negative results obtained in response to visual stimulation were due not only to the long functional inactivity of the visual area but also to the disuse of the corresponding part of the "center of consciousness," and perhaps more to the latter than to the former. It is already indicated by some of Dr. Riesen's experiments that the slowness of the acquisition of visual control by his animals was due to their inability to form conditioned reflexes, that is, to link up the cortical visual area functionally with the "center of con-

sciousness." It could be achieved only if very strong stimuli were used. Two examples of this are given below: A conditioned reflex could not be formed in 1 case, but was formed, though with great difficulty, in the other.

For feeding purposes, as was previously indicated, the dark room in which the 2 infant chimpanzees lived was lighted daily for a short time (from four and one-half to twelve minutes), during which a person wearing a white coat entered the room and moved about. In spite of their receiving this daily visual stimulation with a white object, no corresponding conditioned reflex was formed in the monkeys, although the total periods which the animals spent in the illuminated surroundings during the time they were living in darkness were about forty-five and fifty hours, respectively.

The following experiment was performed on monkeys in daylight. A circular disk painted with bright yellow and black stripes was shown to normal infant chimpanzees and to those which had been reared in darkness. The former reacted to it by displaying fear or otherwise. The latter showed no awareness of the disk whatever. At the next presentation of the disk an electric shock was delivered in the mouth region. The normal chimpanzees at once developed violent avoidance behavior, which was repeated with each successive showing of the painted disk. It was a long time before the corresponding defense reaction was formed in the monkeys reared in darkness.

To translate these facts into physiologic language, the disuse of one of the cortical centers not only rendered extremely difficult the formation of conditioned reflexes, the arc of which passes through this center, but kept the special function of the "center of consciousness" dormant.

There are indications that the same phenomenon occurs in patients after operation for congenital cataract. It takes them weeks to learn to discriminate between such simple patterns as a triangle and a square (von Senden[17]). The inability to use sight when reared in darkness seems to be restricted to man and the primates, since lower vertebrates, for example, rats and chicks, which are subjected to the same treatment and then brought into the daylight at once show themselves capable of visual control (Riesen[16]).

CONCLUSION

The facts here presented undoubtedly show that the physiologic approach of Sechenov, Jackson and Pavlov to the study of the functions of the cerebral cortex was correct. The cerebral cortex is the machinery

17. von Senden, M.: Raum- und Gestaltauffässung bei operierten Blindgeborenen vor und nach der Operation, Leipzig, Johann Ambrosius Barth, 1932; cited by Riesen.[16]

which subserves a special form of reflex action, known as a conditioned reflex. Usually a conditioned reflex act is combined with a conscious perception of the phenomenon in question. None of these three investigators denied that this is the case in man, nor that it is probably true for the higher vertebrates. But all three believed that it had nothing to do with the reflex nature of the cortical processes. In the cerebral cortex the nervous process is initiated by an impulse which arises outside of it. It is not the result of some "psychic" act. The establishment of the reflex nature of the cortical processes permitted functional unification of the whole nervous system from the physiologic point of view.

The theory that the nervous processes in the cerebral cortex are of a reflex nature, being purely physiologic, does not preclude one from assuming that a close cooperation exists between the cortex and the "center of consciousness." It is a fact of common knowledge that conscious perception of things is possible only if the "center of consciousness" functions normally, as, for example, when it is not poisoned or compressed by a tumor. Again, it is known that a conditioned stimulus reaches the "center of consciousness" only when the cerebral cortex is undamaged. But, over and above this, it seems that for the origination of a conscious process conditioned reflex activity of the cerebral cortex is essential. This is evident in the case of more or less simple reactions of the brain. It is most probable that the highest manifestations of the human spirit also require preliminary reflex activity of the cerebral cortex.

Montreal Neurological Institute.

Clinical Notes

A STIMULATOR FOR NEUROSURGERY

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AND
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ELECTRICAL stimulation of the nervous system at the operating table has long been used as a means both of obtaining information to guide the course of the operation in progress and of increasing knowledge of the nervous system. Countless electrical arrangements have been used for stimulation, and much valuable work has been done with extremely simple apparatus. Almost any means of delivering a shock to a nerve may be used successfully, provided the operator is thoroughly familiar with his apparatus and its idiosyncrasies. Most neurosurgeons, however, find it desirable to have some sort of apparatus which is durable and safe, and which can duplicate desired stimulating conditions at any time with a minimum of attention. The instrument here described was designed to fill such a need.

The 60 cycle, approximately sinusoidal, alternating current used in power lines provides a satisfactory, if not ideal, stimulus for the majority of applications in which concurrent recording of action potentials is not desired. It may readily be stepped down to the desired voltage, and its level may be conveniently measured by means of conventional voltmeters or ammeters. It is essential, however, that any stimulator using it be so designed and constructed that there is no danger of accidental application of the full line voltage. The 60 cycle sine wave was chosen as the form of stimulus for this instrument; its safety depends not only on the electrical design but on details of the mechanical construction which make contact of the stimulating leads with the power leads impossible even if all wires in the instrument are broken. As shown in the wiring diagram (fig. 1), the current is passed through two transformers, so that even in the unlikely event that defective insulation should develop the patient would still be protected. The power leads enter an insulated compartment, formed on one side by the "bakelite" subpanel, on two sides by "bakelite" partitions and on three sides by the wooden case. The fuses and power switches are mounted in this compartment, and the power leads leave it through a small hole near the first transformer, to run less than ¼ inch (6 mm.) before they enter under the transformer case. Should they become broken and touch the secondary leads under the transformer case, the patient is still protected by the second transformer. All other leads of any considerable length are run between the main panel and the subpanel, so that if they are broken they remain within the insulated space. All such leads are of insulated wire, being further protected by running in varnished cambric tubing.

From the Department of Anatomy, Cornell University Medical College.

This work was carried out prior to and during contract number (OEM-CMR M-829), between the Office of Scientific Research and Development and Cornell University Medical College.

Consideration was given to a constant current type of output to make the instrument more effective for percutaneous stimulation. Since, however, a sine wave offers some disadvantages for this type of work, and since, in general, a constant voltage type of output with low source impedance is more reliable where direct contact with the nerve tissue is possible, it was decided to employ the latter type and to restrict the recommended use of the instrument to direct contact stimulation.

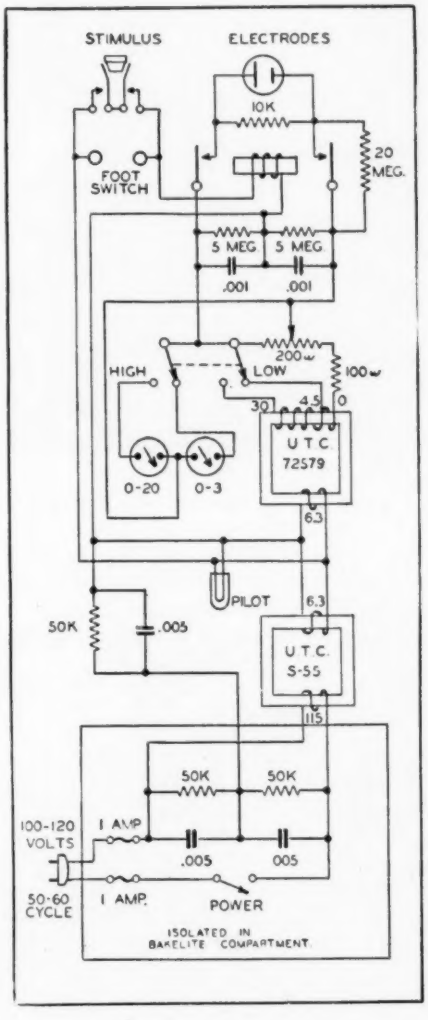

Fig. 1.—Wiring diagram.

Two ranges of output voltage are provided; a low range of 0 to 3 volts, which is adequate for stimulation of peripheral nerve and for most cortical stimulation, and a high range of 0 to 25 volts, which may sometimes be desired for stimulation of the sensory cortex. Separate voltmeters are provided for the two ranges, and the range selector switch connects only the proper meter for the range in use. This arrangement, while somewhat more expensive than a dual

Fig. 2.—View of the instrument from above, with the case open.

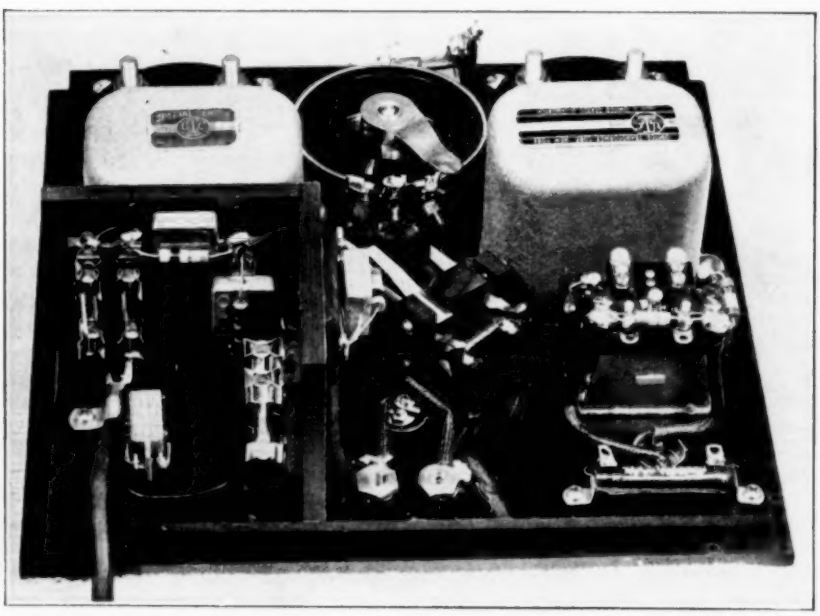

Fig. 3.—View from below of the panel and the subpanel assembly, removed from the case.

range meter, precludes errors which might result from reading the wrong scale. Similar errors might arise from inadvertent use of the wrong range while setting the stimulus according to a scale on the voltage control. For this reason, no scale or reference mark of any kind is provided on the voltage control, and the intensity of stimulus can be set only by reading the proper meter. The source impedance is low enough that the stimulus will ordinarily fall only slightly below this value.

The stimulus is applied through a relay, which may be operated by means of a push button on the panel or by closure of the foot switch terminals. Any type of foot switch that closes a single circuit may be used. The relay is operated from the secondary of the first transformer, so that the foot switch circuit is effectively isolated electrically both from the power line and from the patient. If it is desired to synchronize the stimulus with a signal magnet or other marker on the recording apparatus, it can readily be done by providing a double pole, single throw stimulus switch, using one pole to actuate the marker and the other to close the foot switch terminals of the stimulator.

A high resistance, static charge leakage path to the power line ground is provided, as shown in the wiring diagram. A capacitative path is also provided for radio frequency currents. Mr. John P. Hervey, of the Johnson Foundation, suggested the latter feature.

The power line ground, rather than a separate ground lead, was chosen for the return point of these paths, as it was felt that the increased convenience more than offset the one disadvantage of using the power line ground; namely, that an extremely weak stimulus, transmitted through the leakage paths, is present at the electrodes even with the relay released. In practice, difficulty has almost never been encountered from this source, but in any case in which this weak stimulus is troublesome, it can readily be eliminated by grounding one or the other of the foot switch terminals.

In any piece of electrical equipment used in the operating room, the danger of explosion of the anesthetic, set off by sparking, must be considered. It was felt that any attempt to seal the instrument hermetically might actually increase the danger, as any seal, no matter how perfect, is subject to breakdown, and small quantities of gas which might enter the nearly air-tight compartment through such a leak would comprise a serious explosion hazard. Further, it is impossible to eliminate the possibility of sparking at the electrodes themselves. It was considered preferable, therefore, to provide free ventilation of the instrument, and to state flatly that it is not to be used in the presence of highly volatile and explosive anesthetics, such as ethylene and cyclopropane.

A complete set of operating instructions has been permanently mounted under "lucite" in the lid of the instrument; it includes type numbers of the proper plugs for the electrodes and the foot switch, and of plugs and jacks for electrode extension cords, if these are desired.

The instrument described has been extensively used, with gratifying results, in a large number of neurologic centers of the Army and Navy during the past four years.

Because of the large number of requests for information received from persons who became acquainted with this instrument during the war, it seemed advisable to publish a description at this time.

Cornell University Medical College.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND THE NEW YORK NEUROLOGICAL SOCIETY

Angus M. Frantz, M.D., *Chairman, Section of Neurology and Psychiatry, Presiding*
Joint Meeting, Jan. 4, 1947

Report on a Murderer. Dr. Foster Kennedy.

Dr. Kennedy told of his experience in examining William Heirens, University of Chicago student, accused last summer of the murders of Suzanne Degnan, aged 6; Josephine Ross, aged 43, and Frances Brown, aged 33. He said that murder was not Heirens' actual purpose; his pursuit was chiefly burglary. The boy confessed to "oodles" of illegal entries, "at least five hundred." He was never caught because he did not try to dispose of his loot. Even when he stole a valuable diamond ring, he did not try to sell it. He just "took things and beat it."

At the age of 11, little William Heirens was so upset by the sight of sex antics in a group of boys that he reported the incident at home. His mother, described by Dr. Kennedy as a "prim, buttoned-up woman; a good housekeeper, chic and smart, and a strict Catholic," gave the boy his entire sex education in one sentence: "All sex is dirty; if you touch any one, you get a disease." His father, "an overgrown boy, 6 feet 2 inches," said nothing.

A year later, the now mature lad found sexual excitement in picking women's underwear off clothes lines, hiding in basements and putting it on. At the age of 13 he stopped this because it was easy to slip through doors that he found ajar and to steal things. Next he began to enter open windows. If the mere act of burglary stimulated him pleasurably, the boy left the place intact; if it didn't, he lifted a "token." "It was silly to go in and not take something," he commented. To pique his physical ardor, Heirens specialized in unique thefts. One month he took only war bonds; for a few weeks, only jewelry; for one short period, it was soft cushions.

When, as a first year student at the University of Chicago, the "push" became too great, Heirens invented a fabulous character called "George," who represented to him his own evil self. "I did not really commit burglary; George did it," Heirens repeated time and again. Neither was he responsible for murder; George did that, too. Dr. Kennedy explained that "George" was not seeing double, but was thinking double. The youth fabricated "George" with insight into the fact that he was doing so. He made up "George" so that he, Bill, could go to confession and still not have to tell the priest what he had been doing. Heirens later said he confessed fetishism to the priest, but never murder.

With "George" to take the blame, William Heirens could continue his regular life in his pleasant, comfortable home, in his school, his church and the religious club in which he was prominent. This hysterical fantasy also prevented any one from stopping Heirens from doing what he wanted to do.

To "George," Heirens wrote hundreds of letters, begging the fictional figure not to commit these acts. He also made a weak attempt to prevent himself from "going out," as he termed it. At night in the dormitory, he would disrobe and

hide his clothes in a locker. To regain them, he had to pass through a room where a group of fellow students were gathered. But when the urge became too great, Heirens went out in his dressing gown in subzero weather, walked along an ice-covered sixth floor gutter and climbed down a fire escape to commit a burglary or two.

After strangling Suzanne Degnan and dismembering her body, he placed the remains in several bags and disposed of them in manholes, which he pulled open with his bare hands on a January night—an operation which usually requires a crowbar. Not until a cover fell on his hand, injuring it, and his sexual excitement had duly waned, did he realize that he was hurt. To restir emotional fires, he returned to the basement, or "cutting room," and wrote the ransom note.

Heirens' purpose was not always sadistic. The boy went into many houses where people were asleep, or awake and yet not aware of his presence, without committing murder. "When they spoke to me, I felt a startled reaction," he told the psychiatrists. "Noise sends me off." So, instead of the usual act of retreat, Heirens remained and killed.

Heirens remembered taking the Degnan child out of the window, but did not recall mutilating the body. He said that he felt "vague." "It is like looking through a floor with holes in it . . . trying to look through the holes to see what is below. But there are not enough holes." This description is an excellent picture of a partial amnesic state.

The board's examination proceeded with infinite detail. Heirens' responses to the Rorschach test, his electroencephalogram and his basal metabolic rate were all normal. There was no history of mental disease or epilepsy in the Heirens family.

Physically, he was normal except for an "analgesic cloak" that covered his skin. When a needle was inserted in his finger and under the nail below the white, Heirens felt the needle but no pain. After his murders he usually ate a hearty snack of doughnuts and coffee, went to bed, slept well and appeared at classes the next morning. Yet on dates with girls—and he had had only eight—the youth burst into tears when he tried to embrace them, ran home and could not sleep. Asked by the psychiatrists how he felt when he read stories of his crimes in the newspapers and heard them over the radio, he said: "It wasn't nothing." Despite his university education, he sprinkled his conversation with double negatives. "It was like reading about Russia."

Enormous egocentricity marked entries in Heirens' university scrapbook. Pictures of his heroes—Hitler, Goering and Himmler—adorned the pages. When asked why he preferred them to more exemplary military figures, he retorted: "They [the Germans] knew their onions."

"I wonder how I could run the world," Heirens asked himself in another section of the carefully written book. "It must be wonderful to have that much power. They [presumably the Germans] got it . . . but there must be an easier and faster way to get control."

DISCUSSION

DR. FREDERIC WERTHAM: I am grateful to Dr. Kennedy for having given me the opportunity to look over the voluminous material in this instructive and interesting case. After having gone over all the psychiatric examinations, various psychologic and psychometric tests and full social service reports in this case, I must confess that I personally should have no hesitation in declaring this boy legally insane. According to law, there are various definitions of insanity. They differ in different states—in New York and New Jersey, for example—and they

differ even in the Army and in the Navy. I feel that Heirens' case could fit all the definitions. I must confine myself to a few general comments. I think a boy like Heirens belongs in a psychiatric hospital, and I should have declared him irresponsible according to the legal definition.

Dr. Kennedy and I collaborated a short time ago in an interesting murder case in which a young woman married to a naval intelligence officer killed her two children. There is no doubt that during the commission of this murder the young woman was in a psychotic state, and it happened through our efforts that her case was successfully handled from both the legal and the scientific viewpoint. She was sent to a hospital for the criminally insane, where she belonged; and after a while, when she had recovered from the psychosis, she was discharged and is now free. We agreed on the psychiatric diagnosis of a reactive psychotic state, but on the legal record it is stated differently. In order to get her out of jail and into the hospital for the criminally insane, the Lunacy Commission declared the girl schizophrenic, when we were completely convinced that she was not. Later, at the time of her discharge, the diagnosis was manic-depressive psychosis, recovered. This also was not in agreement with our opinion.

I am telling you of this because I think that this boy of 17, who got into this terrible trouble, had the misfortune not to fall into any of the accepted diagnostic categories. I am sure some people will say he is schizophrenic; and we all realize that he is not. In various reports about him the word "hysteria" is generally used; but if you will reflect for a moment on the last ten hysterical patients whom you have seen, you will admit that such patients do not have sexual satisfaction from going through a window; they do not kill people and dismember them. Heirens' poor mental health is of a different kind. In one of these reports it is stated that the boy is "antisocial." I cannot agree with that. I do not think that psychologically the boy can be called antisocial. He tried everything he could to fight this urge. Dr. Kennedy told you the episode of the locker. He tried to stay with his father and with his roommate. At one time he held on to the bed posts for two hours so that he could not go out and do something wrong. He had a profound conflict, and I received the impression that he was a bright boy, a sincere boy, a warm boy—and a very pathetic figure. He tried to change himself "from an introvert to an extrovert." He tried all kinds of things.

Why could he not solve the conflict? He could not solve it because it was not conscious, because he could not put it into words and could not understand these two factors which were fighting against each other. Psychologically and psychoanalytically, the case is very interesting. There is always the great danger that we as psychiatrists may deal with such a case clad in the lion's skin of Freud, but finally act as though we were dressed in the hair shirt of Kraepelin. It is most important to realize that there is a diagnostic world between such commonly accepted designations as those of manic-degressive psychosis and schizophrenia. Of course, the decision could be gravely abused if one were to say in a case like this that the prisoner is legally insane, but anything can be abused—atomic energy, for instance. This enormous emotional conflict made the boy do terrible things. The question is: Must one think in rigid philosophic terms of quality as one thing and of quantity as another? Is it not true that water can be very cold and still be water, but that there comes a moment when water becomes so cold that it is no longer water, but is ice? If in a patient the emotional conflict becomes so intense as to lead to such disastrous consequences to himself and to other human beings, it can be assumed that quantity changes into quality, and one has a right to call the person psychotic.

William Heirens falls under the legal definition of not knowing the difference between right and wrong. He weeps when he touches a girl's breast. He has the selective feeling of guilt in which he thinks that sex is worse than murder; he is mixed up about right and wrong, and I cannot believe that this 17 year old boy, who had the serious intention of telling the examiners the truth, could confer with a lawyer and make his best defense for behavior which he himself understood so little.

I agree with Dr. Kennedy about the psychologic interpretation of the dual personality of "George M. S.," and I assume that "M.S." stands for "myself." The boy created this figure; so it would be difficult to say what is fabrication and where it begins to assume some kind of psychologic reality. Lawyers sometimes ask whether Heirens would have committed murder if a policeman had been present. I think he carried a policeman within him. He tried to be a rigidly moral boy, and when he went out, he was in an abnormal state: The policeman was not with him and he committed crimes, but he would much rather have done the right thing. That to me is evidence of a serious mental disorder. Psychiatry is handicapped by the formal definition of neurosis. There is a vast field of psychogenic disorders of personality. Cases of the Heiren's type, quite apart from their medicolegal aspects, can teach us a great deal about other problems of psychopathology. We should be grateful to Dr. Kennedy for having placed this case so clearly and so successfully on the psychiatric map.

Dr. Foster Kennedy: I did not tell you the issue of this case. Our report went forward to the Supreme Court, and Heirens pleaded "guilty." We were anxious lest he should plead "not guilty," which would have allowed the trial we had all tried to avoid. He was sentenced to prison for life and was immediately transferred to a hospital, where he is under constant psychiatric observation; so I believe the wise thing was done by all. Had he been pronounced psychotic and irresponsible, it would have been a green light to any one who wanted to do the same thing.

There are two protagonists in every courtroom concerning crime of this kind: the criminal and society. While Dr. Wertham is weeping his tears for "the pathetic figure" of this young man, I should like him to reserve a few for the women who were murdered and the child who was strangled and cut up. Heirens understood his actions so well that he took care in them not to be thwarted. It is said that he could not help himself. He could have gone out and sought aid from a physician, as any obsessional patient does who must wash his hands sixty times a day. He did not want to be thwarted. He liked doing so well what he was doing that he took every precaution not to be stopped. That is his guilt.

Bridging of Nerve Gaps by Lengthening of Central End. Dr. Thomas I. Hoen.

The problem of bridging gaps in peripheral nerves has not been solved by the use of grafts. If any grafts were to be successful, it is felt that homogeneous grafts or fresh cadaver grafts would have been the best chance.

During the early days of the war such grafts were tried in the neurosurgical service of the United States Naval Hospital, St. Albans, L. I., N. Y. Heed was taken of the fact that for a graft to survive it must be in a good bed, where it can receive circulation from contiguous tissues. In spite of every care, none of the grafts were successful, and study of the material disclosed that while axonization occurred for a short distance into the graft, the remainder of the graft became collagenized and fibrotic and the outgrowing fibers became lost in scar tissue.

Analysis of the results of end to end sutures in the service disclosed that a large percentage of the failures comprised a group of cases in which the distal end of the severed nerve had been placed under considerable tension, and microscopic section of the peripheral end in these cases showed loss of the normal internal topography with collagenization of the schwannian tubes. No such alteration occurred in the central end of the nerve, which had been put under similar tension. These observations led to the supposition that the central end of a severed nerve, which is a normal structure in every way, might tolerate considerable stretching over a prolonged period.

In a group of cases in which the gaps between the severed ends of the nerve were of too great a magnitude to permit end to end suture, a procedure was employed which is briefly presented as follows: In a first stage operation, the distal end was not disturbed, but the central neuroma was fixed to a traction wire suture. Traction was then applied by various methods, depending on such factors as the position of the lesion and the flexibility of adjacent joints. It was found that over a period of weeks, considerable lengthening of the central end could be obtained and an end to end suture carried out at a later stage.

During the past year and a half, 13 patients have been subjected to this procedure. Even though sufficient time has not elapsed to permit a final evaluation, signs of reaxonization of the distal end of the nerve are already apparent in 11 of the 13 cases.

It is felt that this lengthening should not be considered as stretching, since the increase in length occurrs without any microscopic evidence of alteration of the structure of the nerve and since the gain in length is considerably in excess of that usually assessed as the limit of stretch (in 1 case, 40 cm. of nerve was increased to 60 cm.). It is believed that actual growth occurs under the stimulus of stretch.

DISCUSSION

Dr. John E. Scarff: Dr. Hoen has presented his material in such detail that there is little to add to the discussion other than my personal appraisal of this work. In my opinion, this contribution is the most provocative, and may well prove to be the most important, contribution that has been made to the surgery of peripheral nerves since World War I. I wish to congratulate Dr. Hoen on what I consider a splendid contribution.

Dr. Joseph E. J. King: This paper represents the only technical improvement of any importance since the first world war and is by all means the greatest recent contribution in the field of peripheral nerve surgery of which I have heard. I agree that the nerve grafts were complete failures, and Dr. Hoen stated his reason for the failures. Regardless of their success in dogs and cats at Ann Arbor, these grafts are not effective in human beings, and he stated why. If there is a large loss of nerve, there is also a large loss of soft parts, with no place to put the graft. The main fact is that nerve grafting did not work, and the only thing that could be done when the nerve could not be brought together properly was tendon transplantation. Dr. Hoen's method of lengthening the proximal end is extremely clever, and putting the torpedo head in front of the neuroma to make way for the oncoming neuroma is most ingenious. In World War I, we did all the things he mentioned—shortening bones and transplanting nerves, thus making it possible to close a great number of defects—but his closing of that enormous defect is remarkable. In his last case the injury occurred in 1943, and a long time had elapsed; nevertheless, the patient has some return of function—not yet complete—and it is astonishing. There are three reasons for the good results: (1) He

took up slack of the already contracted nerve; (2) the nerve doubtless grew to some extent, and (3) there was an element of stretching. These three factors must be considered. Dr. Hoen's method is the most ingenious I have yet heard of for lengthening the proximal end.

DR. FOSTER KENNEDY: May I congratulate Dr. Hoen on his inventive genius, with the demonstration of good principles and great mechanical ability; but may I ask whether he has had time to learn the clinical results?

DR. THOMAS I. HOEN: To answer Dr. Kennedy first: Of my 13 cases, 1 was lost; no result was apparent in another, and there is some evidence of regeneration in 11. In all 11 cases, Tinel's sign was present well down beyond the gap; in 9 cases there was electrodiagnostic evidence of reinnervation of the muscles, and in 6 cases there was actual recovery of voluntary movement. It should be remembered that in all these cases the repair was done within the last year and that in the normal course of a peripheral nerve suture one should not expect to have a final result in less than a year. Evidence of the rate of recovery in these cases following the last stage of operation has paralleled the rate of recovery in cases of ordinary, simple nerve repair.

Dr. King's analysis of the mechanism of gain in length, by taking up slack, (2) by stretch and (3) by growth, is of course the crux of the problem. We know that when traction is applied to these nerves, the nerve end will descend 1 to 2 cm. the first day, thus taking up slack; in the next few days more lengthening occurs, probably exerting stretch. However, the additional length which is obtained by peripheral traction, I believe and hope, is growth.

Book Reviews

The Criminal and His Victim. By Hans von Hentig. Price, $6. Pp. 461. New Haven, Conn.: Yale University Press, 1948.

The author, formerly professor of criminal law and criminology at the University of Bonn; teacher at the State University of California, Oregon, Iowa and Colorado; director of the Colorado Crime Survey, and at present professor of sociology at the University of Kansas City, attempts in this book to cover a wide number of subjects in the field of criminology. At the outset, he makes the following postulation, "It is futile to argue causative predominance of constitution over environment or vice versa. Since crime is mostly the result of group conflicts, the social etiology must prevail." While the integration of sociology and psychiatry in the understanding of the problem of crime is well acknowledged, the contention that sociologic factors dominate does not coincide with psychiatric experience. This conclusion is contrary to the clinical findings of psychiatrists in the field of criminal psychopathology, in which the case study of the individual patient, with his complex makeup and his conflicts, especially around his instinctive drives, discloses from a dynamic standpoint that such components as emotional maturity and stability, neurotic factors and psychosexual maladjustments play a much greater and more basic role than social factors, which may to a certain extent have a precipitating or conditioning influence. The author emphasizes the sociologic approach in understanding criminal conduct, as against the psychiatric method of studying the dynamics of behavior in the individual delinquent. Crime as a social phenomenon has many facets, among them, the environmental, cultural, economic and legalistic. None of these factors, as studied in various surveys and investigations, has given any adequate understanding as to why many persons form antisocial patterns of behavior in such settings. The motivation behind such activity has been frequently disclosed by psychiatric probing.

The book is divided into four parts: constitutional factors and crime; sociobiologic elements of crime; geophysics and crime, and the victim. The range of subjects covers such material as the influence of parents on constitution; criminality and mental disorders or defect in the offspring; prenatal influences, and such factors as birth trauma, premature birth, order of birth, twin births and heredity. There is a 55 page chapter on physical traits and peculiarities, in which considerable space is devoted to the description of various colorful, muscular types among prize fighters and gangsters, though psychologic factors played no role in their aggressions. There is also a long discourse on the relation of red hair to crime, without any particular conclusion concerning the connection between red hair and antisocial activity. Lombroso, with his discredited criminal anthropology, is cited freely, especially on the subject of left handedness. There is also a discussion of the psychology of the deaf and the blind, and that of strabismus and stuttering.

In the chapter entitled "Psychological Variables," in which are discussed such topics as intelligence, tattooing and slang, the author speaks of a "psychology of specific criminal types," a concept which is far removed from the widely accepted psychiatric approach of the study of the specific individual in antisocial behavior. Most of this chapter is devoted to an interesting account of the colorful vocabulary employed by criminals.

From the chapter of 63 pages on "Mental Disorders," a few quotations will illustrate the lack of expert training and knowledge in this field and the confusion in the use of psychiatric terminology. Most of the material is obtained from various publications, with failure to employ many well known, more modern and authoritative sources from the psychoanalytic and psychiatric literature. "Insanity is an exaggerated normality." "Epileptic insanity is a psychosis in which defective heredity, syphilis, rheumatism, diabetes and other ailments are the predisposing conditions." "There is an intoxication of endocrinal origin" (citing Kraepelin's material as to the etiology of schizophrenia). "Many pimps and prostitutes are schizoid." In this discussion, "schizophrenia" and "schizoid" apparently mean the same thing to the author. He quotes from the German and the Italian literature, including Lombroso, and agrees with these writers that there exists "something called moral imbecility and constitutional immorality," concepts and terms which are now obsolete, in the light of modern psychiatric knowledge. Again, he quotes Kraepelin to the effect that "59% of the schizophrenics end up in pronounced mental deterioration and 27% in dementia of a lighter grade." Nothing is said about modern statistics concerning the large percentages of recovery and improvement following shock therapy. It is noted that the term "psychopath" is employed to denote the psychotic person—another example, among others, of loose and inaccurate psychiatric terminology. In relation to the amount of descriptive matter in the field of mental disorders, little is brought out concerning the relation of mental disorders to antisocial behavior or in regard to the psychodynamics. The impression is gathered that the various concepts and conclusions made by the author are primarily the material gathered from an extensive bibliography, and not from his own analyses founded on personal examination of criminals. While consideration is given to the mental and physical effects of mariahuana and peyote, nothing is mentioned of their influence on antisocial behavior, an omission which is indeed surprising in view of the controversies and the intensive investigation concerning the question whether mariahuana has been a causative or precipitating factor in connection with crime. The author makes the statement that "sexual aberrations, homosexuality in particular, cannot be discussed in a book on crime." This is a rather surprising assertion in view of the large number of sexual offenders and the crimes of murder, robbery, assault and larcenies which have a homosexual component as a driving factor.

The most valuable contribution of this book, and by far the most interesting, is contained in the last chapter (67 pages), entitled "The Contribution of the Victim to the Genesis of Crime," in which many criminal activities are shown to depend in great measure on the subject-object relation. This chapter discusses the activities of the confidence man and the suggestible victim who has "larceny in his heart." Psychiatrists experienced in the field of criminology frequently encounter the immature, the suggestible and the mentally defective person used by criminals as a victim or a partner in crime. Psychiatrists have pointed out, to mention only a few examples, that seductive practices of some minor girls have occasionally provoked sexual offences against them, and the homosexual person seeking a homosexual partner may become the victim of robbery, assault or blackmail. While this is not a new contribution, the detail and emphasis offered here make this chapter a welcome addition to the field of criminology.

Die Angst des Kindes. By M. Loosli-Usteri. Price, 15 francs. Pp. 164. Bern, Switzerland: Hans Huber, 1948.

The author of this book is a psychologist, and the present work is a psychologic and educational study of the problem of infantile anxiety. The author tries to clarify the theoretic concept of anxiety. She postulates the existence of an

objectless, "free-floating" anxiety, the "anxiety as such." This is a state of unrest and uncertainty which is the expression of a disturbed equilibrium between two opposing forces in the child, the tendency to progress and the desire for stabilization. This state of anxiety is a normal phenomenon, and the first emotional reaction of the child. The author's view is based on Jung's concept of the "collective unconscious."

The objectless "anxiety as such" forms the nucleus of all other manifestations of anxiety and may become crystallized in three forms: (*a*) an anxiety of tions of anxiety and may become crystallized in three forms: (*a*) an anxiety of short duration, but great intensity, associated with a feeling of oppression and resulting in a complete, but transitory, disturbance of the balance of the personality; (*b*) an anxiety referred to an object. This state of mind is called an emotion. A distinction is made between a normal anxiety in view of a threatening danger and an irrational anxiety based on an imaginary threat, and (*c*) fear, which contains an element of expectation and is considered as a feeling. Here, again, a differentiation is made between a realistic and an irrational basis of this reaction. In fear, the struggle between the two opposing forces occurs on a more intellectual level. Since the author accepts the idea of the collective unconscious, she considers the free-floating anxiety as part of it, and therefore as being of an overindividual nature. The other types of anxiety, if repressed, become part of the individual unconscious.

From infancy to adolescence the child passes through various phases of anxiety. At puberty new energies appear and lead to a considerable increase of anxiety.

How does the child fight against anxiety? In early childhood evil forces are fought by magic; symbols and projection of fears to persons or objects in daydreams and phantasies play an essential role. At a later age stories and movies serve the purpose of abreaction. The child exposes itself to really difficult situations in order to acquire courage and to master anxiety. Anxiety thus poses a serious problem to the educator. He has to support the child in its fight against this imagined threat and to establish a healthy balance between the dynamic and the static forces in the growing personality. The main issue is to create confidence in the child, in itself and in its environment. As therapy, the author recommends play technic, drawings and the encouragement of phantasies. She warns against intellectual interpretations and exaggerated introspection. The question of the positive function of anxiety is raised; this role is found in its restraining influence on the dynamic powers in the personality. In addition, anxiety increases the alertness of the child, necessitates a constant readjustment to the environment and thus favors intellectual development.

Th theories developed appear speculative. The assumption of a useful role of anxiety in the way suggested by the author and her classification of the various forms of anxiety may be questioned. However, the parts dealing with the therapeutic and educational aspects of the problem are valuable. The author has a warm understanding of the child's mind and conflicts, and the book will be of interest to the educator and the therapeutist.

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